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Effect of Insulin Therapy in Type-2 Diabetes in Improving B-Cell Function and Glycemic Control Compared with Oral Anti- Diabetic Agents with or without Insulin in Routine Clinical Practice

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Abstract

Observational studies are valuable tools for assessing the applicability of results from randomized controlled trials to broader patient populations. They are especially important in chronic diseases such as diabetes, as they can provide a comprehensive picture of the safety and effectiveness of a particular therapy across cultures and phenotypes.The aim of this study is to determine Efficacy, Safety and Tolerability of the early intervention of insulin treatment with or without Oral Anti Diabetic's (OAD) in type 2 diabetes for improving glycemic control compared with OAD's alone and to determine the persistence of effect up to 6 months in the intervention group in routine clinical practice. The effect of the anti-diabetic agents will be measured by monitoring the Fasting blood glucose level (FBG), Post prandial blood glucose level (PPBG), Glycated hemoglobin levels, C-Peptide levels and all other necessary parameters needed for diabetic management.

Key words: *Type 2 Diabetes, Oral Anti Diabetics, Fasting Blood Glucose Level*

INTRODUCTION

The prevalence of diabetes mellitus has dramatically increased in recent years in India, an estimated 40 million nationwide have diabetes. A similar, disproportionate number of hospitalized patients have diabetes. In the recent, the prevalence of diabetes in hospitalized adults is conservatively estimated at 12.4%- 25.0% and for every two patients diagnosed with diabetes in the hospital, there may be at least one other patient in the hospital with unrecognized diabetes, who is at risk for poor outcomes and safety issues, as well as higher health care costs. However, the prevalence and an accurate estimate of the number of patients admitted to hospitals with diabetes have never been reported because Type 2 diabetes is under diagnosed in hospital setting.

The prevalence of diabetes is increasing in India, but glycemic control appears to be deteriorating. Glycemic control remains the major therapeutic objective for diabetics. Although type 2 diabetes is a progressive disease, patients in the early stages of diabetes may advance at different rates. While prior studies have identified factors predicting glycemic control among patients with type 2 diabetes on therapy, we have not found studies that have examined predictors of disease progression in patients with A1C >7% and not on medication therapy. Moreover, no studies have addressed this question in the "usual care" outpatient setting, where most patients first diagnosed with type 2 diabetes are initially managed. Furthermore, no recent studies have examined the factors associated with early initiation of glucose-lowering medications.

As a result of the landmark United Kingdom Prospective Diabetes Study (UKPDS), the clinical importance of glycemic control in patients with type 2 diabetes is well established. The American Diabetes Association (ADA) estimates that the risk of diabetes-related mortality increases 25% for each 1% increase in HbA1c. Each percentage point increase in HbA1c has also been estimated to correspond to a 35% increase in the risk of micro vascular complications and an 18% increase in the risk of myocardial infarction (fatal plus non-fatal).

Despite evidence that normalizing blood glucose levels as far as is practicable minimizes the risk of diabetic complications, glycemic control in patients with type 2 diabetes is commonly poor in routine clinical practice. Traditional therapy for patients with type 2 diabetes has primarily focused on controlling FPG levels with one or more oral anti-diabetic drugs (OAD's) and/or basal insulin. Although both fasting and postprandial blood glucose levels contribute to glycepmic control, these

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	First visit	3rd Month	6th Month
Monitoring Parameters	Height/ Body wt	Height/ Body wt	Height/ Body wt
	Blood pressure	Blood pressure	Blood pressure
	BMI	BMI	BMI
	Blood sugar levels	Blood sugar levels	Blood sugar levels
	Random	Random	Random
	FBG	FBG	FBG
	PPBG	PPBG	PPBG
	OGTT	HbA1C	OGTT
	HbA1C	Hypoglycemia	HbA1C
	Hypoglycemia	Hyperglycemia	Fasting C-Peptide
	Hyperglycemia		Hypoglycemia
	Complications		Hyperglycemia
	Medication regimen		Complications
			Medication regimen

RESULTS

The aim of this study was to assess effect of insulin therapy in type 2 diabetes in improving β-cell function & glycemic control in routine clinical practice. Patients with newly diagnosed type 2 diabetes who required insulin as per the physician's decision based on the biochemical profile (if FBG> 200mg/dl or PPBG > 300mg/dl or HbA1C > 9%) were all included in this study. A total of 450 type 2 diabetic patients were recruited out of 600 screened. Out of the total study, 319 patients received complete 6 month course of treatment with regular follow-up, in these 97 patients on insulin mono-therapy, 88 patients on combination insulin + OAD and 134 patients on OAD alone received complete six month course of treatment.

Demographics and Disease character were shown in Table-1. Totally, 207 male and 112 female patients with the mean age (years) of 48.11 ± 8.33 and body weight (kgs) of 65.7 ± 9.79 were included in this study (Table - 1). Mean blood glucose level, presenting symptoms (%) and complications (%) at the time of recruitment were reported in Table -1.

Glycemic Control

Glycated Hemoglobin Level (HbA1C)

In the study Insulin treatment was compared with insulin + OAD and OAD alone in newly diagnosed type 2 diabetes with severe hyperglycemia. The patients were recruited with mean HbA1c of more than 9.00%, after 6 month intensive insulin therapy results showed that, the HbA1C level (Figure - 1) was significantly lower in the insulin group than in the insulin + OAD than OAD's (6.73 ± 0.99% Vs. 6.81 ± 1.02% Vs 7.44 ± 1.04%; (P = 0.0001). Our data suggests that, at the end of 6 months treatment HbA1C levels with insulin group < insulin + OAD < OAD alone (Table -2). It indicates that, the optimal blood glucose level was very well controlled with insulin group as compared to insulin + OAD or OAD alone.

Blood Glucose Levels

Fasting Blood Glucose (FBG)

The patients recruited with mean FBG of > 200 mg/dl, at the end of 6th month, FBG levels (Figure - 2) were almost similar in all three groups (85.505 ± 13.085 Vs 85.11 ± 13.949 Vs 86.694 ± 14.052; P = 0.8875). Our data suggests that, at the end of 6 months treatment the average reduction in fasting blood glucose levels were high with insulin group (132.72 mg/dl) as compared to insulin + OAD (128.65) or OAD alone (88.64 mg/dl) (Table - 2).

Post Prandial Blood Glucose Level

The patients were recruited with mean PPBG of more than 200 mg/dl, at the end of 6th month, PPGB levels (Figure - 3) were almost similar in all three groups (136.16 ± 29.088 Vs 136.07 ± 28.00 Vs 137.66 ± 28.84; P = 0.9927). Our data suggests that, at the end of 6 months treatment the average reduction in postprandial blood glucose levels were high with insulin group (263.81 mg/dl) as compared to insulin + OAD (254.88 mg/dl) or OAD alone (188 mg/dl) (Table - 2).

Oral Glucose Tolerance Test Levels (OGTT)

The study suggests that, at the end of 6 months treatment

2-hours OGTT levels (Figure-4)significantly reduced in Insulin group as compared to combination of Insulin + OAD and oral anti-diabetic agents alone (389.67.53 ± 47.05 Vs 421.72 ± 64.27 Vs 382.1 ± 73.17; *P < 0.0001*). The data suggests that, at the end of 6th months insulin group has greater influence in controlling 2hrs-OGTT level as compared to insulin + OAD or OAD alone.

C- Peptide Level

At the end of 6 months treatment, Fasting C-Peptide level (Figure – 5) was significantly high with insulin group as compared to combination Insulin + OAD and OAD's (1.0312 ± 0.191 Vs 0.9684 ± 0.133 Vs 0.8976 ± 0.097; *P* = 0.0013). The data demonstrates that, in the early intervention of insulin treatment significantly preserves the β-cell function, and it improves the insulin secretion as compared to insulin + OAD and OAD alone.

Adverse Events

Hypoglycemia

At the end of 6 months treatment, percentage of hypoglycemia reported insulin group (15.46%), combination of insulin + OAD (22.72%) and OAD (4.47%) (Table - 2). No severe hypoglycemia occurred in either group. The overall rate of minor hypoglycemia showed no significant difference between these groups.

Weight Gain

At the end of treatment there was no significant difference in body weight from theses treatment groups, insulin. (66.87 ± 9.41) Vs insulin + OAD (64.07 ± 9.09) Vs OAD alone (64.99 ± 9.97); (*P* = 0.1336). But there was a small increase in body weight in the insulin group from baseline to the end point (Table - 2).

Table.1: Demographics & Disease characteristics at the time of Recruitment

Parameters	Group I (n=97)	Group II (n=88)	Group III (n=134)
Male (%)	65 (67.01)	59 (67.04)	83 (61.94)
Female (%)	32 (32.98)	29 (32.96)	51 (38.06)
Mean age (years±SD)			
Male	49.16 ± 8.79	50.57 ± 8.59	48.80 ± 8.82
Female	46.22 ± 8.81	46.33 ± 9.40	47.60 ± 8.73
Body Wt in kgs ± SD	66.56 ± 9.93	64.86 ± 9.32	65.68 ± 10.14
Family History of Diabetes (%)	21 (21.64)	17 (19.31)	26 (19.40)
Mean Blood Glucose level ± SD			
FBG (mg/dl)	218.34 ± 61.14	214.36 ± 59.86	175.38 ± 28.49
PPBG (mg/dl)	394.94 ± 94.78	386.95 ± 92.35	321.73 ± 18.34
HbA1C (%)	9.61 ± 1.65	9.66 ± 1.67	9.28 ± 1.04
Presenting symptoms at the time of detection (%)			
Polyurea	56 (57.73)	42 (47.72)	72 (53.73)
Nocturia	26 (26.80)	14 (15.90)	33 (24.62)
Giddiness	15 (15.46)	32 (36.36)	12 (8.95)
Polyphagia	12 (12.37)	8 (9.09)	21 (15.67)
Polydypsia	17 (17.52)	6 (6.81)	14 (10.44)
Tiredness	42 (43.29)	38 (43.18)	63 (47.01)
Weight loss	13 (13.40)	7 (7.95)	16 (11.94)
Abdominal pain	6 (6.18)	4 (4.54)	12 (8.95)
Numbness	12 (12.37)	8 (9.09)	17 (12.68)
Complications (%)			
Hypertension	6 (6.18)	5 (5.68)	7 (5.22)
CV Events	3 (3.09)	2 (2.27)	5 (3.73)
Pain in limbs	6 (6.18)	2 (2.27)	8 (5.97)
Oedema	2 (2.06)	3 (3.40)	2 (1.49)
Respiratory Disorders	-	-	2 (1.49)

Table.2: Biochemical of the study subjects at the end of 6 months treatment.

Parameters	Insulin alone (n=97)	Insulin + OAD (n=88)	OAD Alone (n=134)
Mean Blood Glucose level			
FBG (mg/dl)	? 132.72	? 128.65	? 88.69
PPBG (mg/dl)	? 263.08	? 254.88	? 188.68
HbA1C (%)	? 2.88	? 2.85	? 1.84
2-hrs OGTT (mg/dl)	? 141.86	? 34.02	? 16.07
C-Peptide Level	1.0312	0.9684	0.8967
Adverse Events			
Hypoglycemia (%)	15.46	22.72	4.47
Body Wt in kgs ± SD	? 66.87 ± 9.41	? 64.07 ± 9.09	?64.99 ± 9.97

Fig.1: Comparison of HbA1C levels at the end of six months treatment.

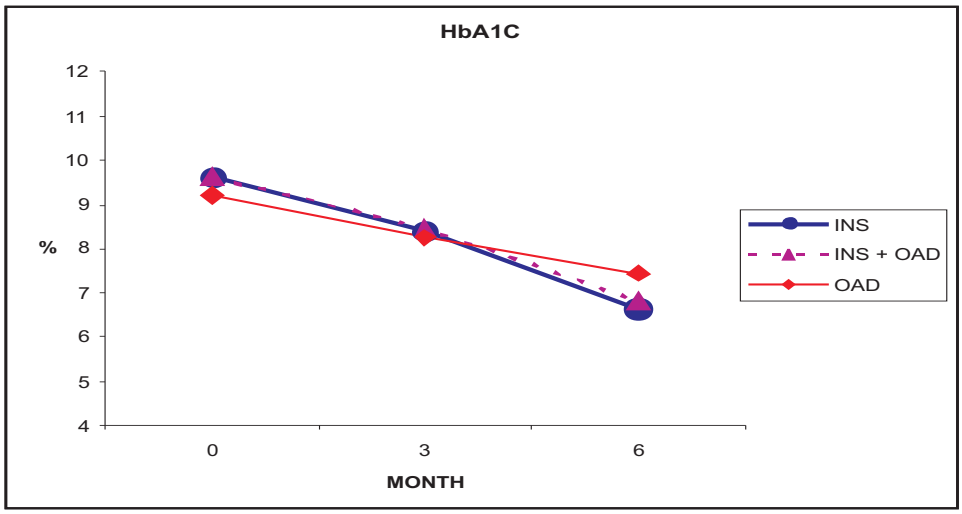


Fig.2: Comparison of FBG levels.

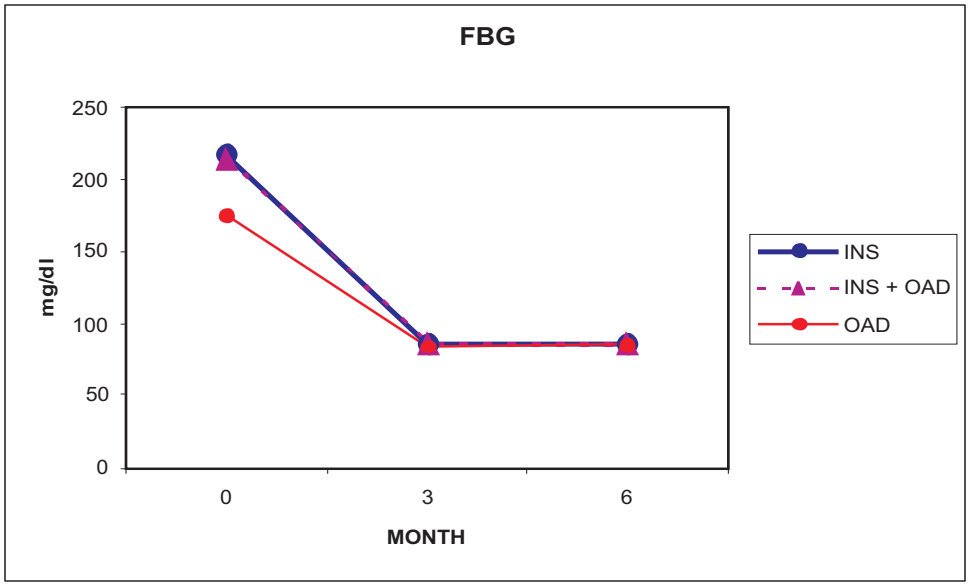


Fig.3: Comparison of PPBG levels

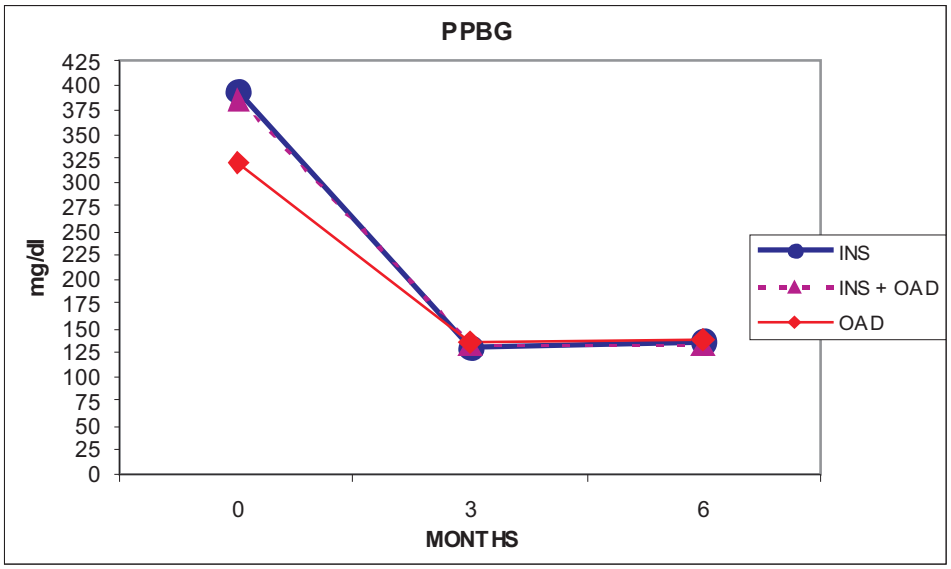


Fig.4: Comparison of OGTT Levels

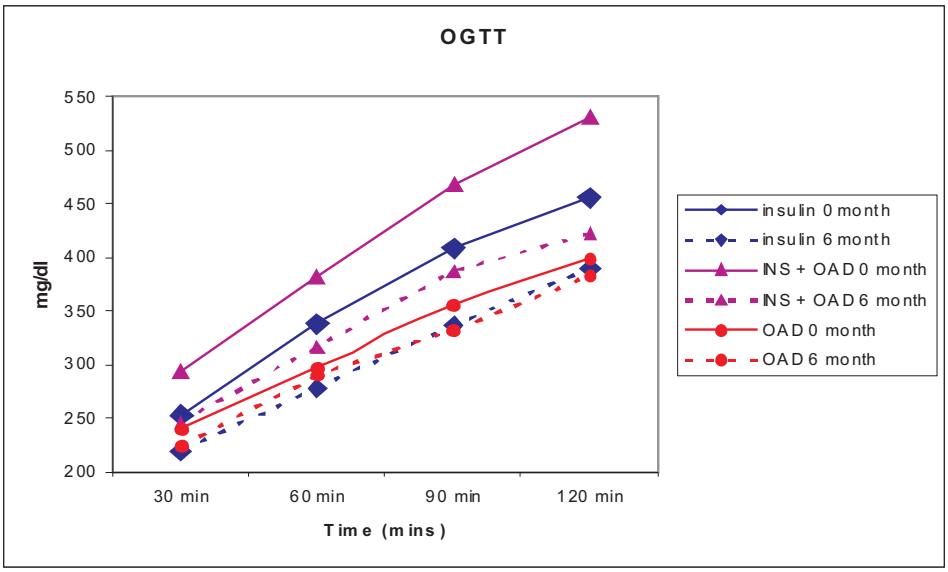
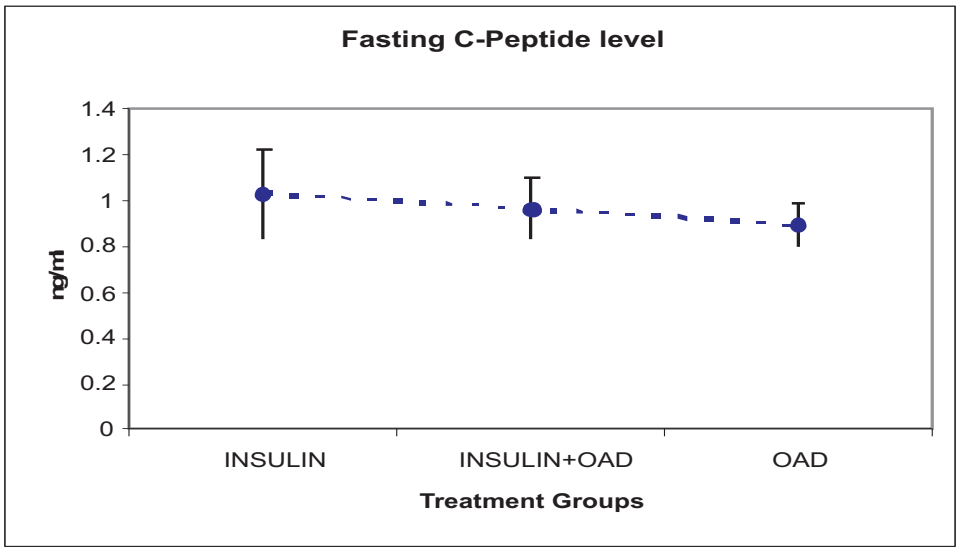


Fig.5: Comparison of fasting C-Peptide level at the end of 6 month treatment



DISCUSSION

Insulin resistance and impaired insulin secretion are the main pathophysiological defects responsible for the development of hyperglycemia in type 2 diabetes. [4,5] With the continuous presence of insulin resistance, progressive loss of β-cell function is the crucial defect. The continuous decline in β-cell function is affected by glucotoxicity generated by hyperglycemia and lipotoxicity due to lipolysis [6]. Impaired β-cell function appears to be reversible, particularly in the early stage of the disease, when the limiting threshold for reversibility of decreased β-cell mass has probably not been passed. So the potential benefits of early, aggressive intervention with insulin treatment to counter both β-cell dysfunction and insulin resistance must be considered. Several reports have shown that short-term intensive insulin therapy can induce long-term glycemic control in newly diagnosed type 2 diabetic patients with mild to moderate hyperglycemia [7,8]. However, more than half of these patients require oral anti-diabetes drug (OAD) therapy within 1 year to maintain normoglycemia.

Newly diagnosed diabetes patients often get their C-peptide levels measured as a means of distinguishing type 1 diabetes and type 2 diabetes. C-peptide levels are measured instead of insulin levels because insulin concentration in the portal vein ranges from two to ten times higher than in the peripheral circulation. The liver extracts about half the insulin reaching it in the plasma, but this varies with the nutritional state. The pancreas of patients with type 1 diabetes is unable to produce insulin and therefore they will usually have a decreased level of C-peptide, whereas C-peptide levels in type 2 patients are normal or higher than normal. Measuring C-peptide in patients injecting insulin can help to determine how much of their own natural insulin these patients are still producing. C-peptide is easily detected because antibodies that are sensitive to it are readily available, whereas antibodies to insulin are much more difficult to obtain. Can be used for identifying factitious disorder, Hypoglycemia with low C-peptide level may indicate abuse of insulin.[42]

When a new-onset type 2 diabetic patients presents with severe hyperglycemia, there are defects in insulin secretion and action, which is optimally treated with aggressive insulin injections, after the symptoms have been relieved, it may be possible to withdraw insulin and shift to oral agents[1]. We hypothesized that continuous insulin therapy for 6 months in new-onset type 2 diabetes with severe hyperglycemia may have a prolonged glycemic control. To address this concept, we designed this 6-month study to evaluate whether treatment with insulin is advantageous compared with Insulin + OAD's and OAD's alone in newly diagnosed type 2 diabetes with severe hyperglycemia.

Glycemic Control

Blood Glucose level

There has emerged evidence that short-term intensive insulin therapy in newly diagnosed type 2 diabetes could improve glycemic control associated with improved insulin secretion [8-10]. Ryan et al. [9] recently reported that, in 16 newly diagnosed type 2 diabetic case subjects with moderate hyperglycemia (mean fasting blood glucose of 239 mg/dl), a 2- to 3-week course of intensive insulin therapy was able to maintain good glycemic control at 1 year in seven of the subjects. In a similar study [10], 138 newly diagnosed type 2 diabetic patients with fasting blood glucose >200 mg/dl (mean fasting blood glucose of 268 mg/dl, peak blood glucose of 390 mg/dl) were hospitalized and treated with continuous subcutaneous insulin infusion for 2 weeks. Optimal glycemic control was achieved within 6.3 ± 3.9 days in 126 patients. In patients with moderate hyperglycemia, a 2-week course of intensive insulin therapy achieving near-euglycemia might induce long-term glycemic control. This result may not be suitable in patients with severe hyperglycemia, such as our subjects with mean initial fasting blood glucose of >200 mg/dl and postprandial blood glucose of >300 mg/dl.[9]

All of our study subjects had received 6 month intensive insulin therapy to make sure the glycemic control was optimal. After recruitment, almost all of the patients were unable to maintain euglycemia without medication. (Table - 2)At the end of 6 months treatment, insulin group showed significant reduction in mean fasting and postprandial blood glucose levels as compared to combination of insulin + OAD and OAD alone. Our data revealed that 6 months of intensive insulin treatment with near-normoglycemia cannot maintain good glycemic control lasting for a long period. We suggest that short-term intensive insulin therapy may induce long-term glycemic control in newly diagnosed type 2 diabetes with moderate hyperglycemia but not in patients with severe hyperglycemia. With this evidence, further treatment with insulin for at least 6 to 12 months was necessary to maintain the euglycemia and improve β-cell function.

Glycated Hemoglobin Level (HbA1c)

In the study patients were recruited with mean HbA1c level of >9% (Table 1). HbA1c values improved from baseline for patients in each interval of the study. Mean values decreased by 2.88% for patients treated with insulin alone, by 2.85% to for patients treated with insulin + OAD, and by 1.8% for patients treated with OAD alone (Table 3). Since the patients in the OAD group did not achieve the same glycemic target as the insulin group. At the end of the study our data suggests that mean HbA1c level was significantly lower in insulin group as compared to combination of insulin + OAD and OAD alone.

Fasting C-Peptide Level

Fasting C-Peptide level was measured at the end of six months treatment and mean values were high with insulin group as compared to combination of insulin + OAD and OAD alone. All these values were with in normal limits and it indicates that, the favorable effect of insulin treatment on endogenous insulin secretion in our study could be due to better glycemic control. Glucose toxicity has been demonstrated clinically and has been investigated extensively in the laboratory. Defects in insulin secretion have been documented and directly related to hyperglycemia and are correctable with the establishment of euglycemia. Thus, the shorter the period of antecedent glucotoxicity, the more likely the full recovery of β-cell function. Our results do support the concept that correction of hyperglycemia can improve insulin secretion. Another possibility is that β-cell secretory capacity may have been restored by "rested" β-cells induced by insulin injection. In our study, most of the subjects required pharmacological therapy to maintain near-euglycemia after discontinuing insulin therapy.

Adverse Events

Hypoglycemia

No severe hypoglycemia occurred in either group. (Table - 2) Over all percentage of hypoglycemia reported insulin group (15.46%), combination of insulin + OAD (22.72%) and OAD (4.47%). The overall rate of minor hypoglycemia showed no significant difference between these groups.

Weight Gain

Insulin therapy is frequently accompanied by weight gain. The mechanisms of weight gain are not fully understood.[14] Improved glycemia due to insulin treatment promotes weight gain by decreasing both the basal metabolic rate and glucosuria.[14-19] However, newly insulin-treated patients with type 2 diabetes gain weight only during the first 2 to 3 years after the start of insulin therapy; in most cases their weight stabilizes thereafter.[19-22] At the end of 6 months treatment, insulin group shows marginal increase in the body. It may due to restoring the physiological function by optimizing the blood glucose

levels (Table - 2).

CONCLUSION

In conclusion, a 6-month course of insulin mono therapy, compared with Insulin + OAD and OAD's monotherapy treatment, could more effectively maintain adequate glycemic control accompanied with significant improvement of β-cell function. Therefore, in the routine clinical practice, management of newly diagnosed type 2 diabetic patients with severe hyperglycemia, strong consideration should be given to early, aggressive insulin mono therapy for at least six months for a rapid and sustained effect on glycemic control and β-cell function and monitoring C-Peptide levels are very important in patients injecting insulin can help to determine how much of their own natural insulin these patients are still producing.

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