**ORIGINAL ARTICLE**

# Efficacy of Adding Single Dose of Intermediate Acting Insulin at Bed-Time in Patients Receiving Maximum Doses of Oral Hypoglycemic Agents

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## ABSTRACT

**Aim:** To determine the effectiveness of adding single dose of intermediate acting insulin at bed-time in patients receiving maximum doses of oral hypoglycemic agents.
**Setting:** Department of Medicine, Services Hospital, Lahore.
**Methods:** A total of 30 cases of type-2 DM uncontrolled on maximum doses of oral hypoglycemic with BMI in between 25 to 42, HbA1c in between 8% to 12%, fasting blood glucose> 126mg on screening were included in the study. Fasting and random blood sugar level and HbA1c was recorded. A single dose of intermediate acting insulin (NPH) was added at bed-time to uncontrolled diabetics already on maximum dose of oral hypoglycemia drugs. Starting dose of NPH was 12 units and titrated according to the fasting and random blood glucose level. Each patient was followed-up twice weekly for one week and then fortnightly for 3 months.
**Results:** The age ranged from 35-60 years with mean age being 46.0±7.9,15 male (50%) and 15 female (50%). The HbA1c levels at baseline and 12th week recorded as 9.20±.40 and 7.13±0.
**Conclusion:** Early addition or switch over of insulin to the already regime help achieve and maintain the goal glycemic control.
**Keywords:** Diabetes mellitus, single dose of intermediate acting insulin at bed-time, efficacy

## INTRODUCTION

Diabetes mellitus is morbidity with a disordered metabolism and inappropriate hyperglycemia either due to deficiency of secretion of insulin or having a combination of insulin resistance and inappropriate secretion of insulin to compensate.

Worldwide, the frequency of diabetes mellitus (DM) in adult population was estimated to be 4.0% in 1995 while it was expected to rise to 5.4% by the year 2025[1].

Various complications of diabetes mellitus (DM) include microvascular complications e.g. retinopathy, renal disease, and peripheral neuropathy, as well as macrovascular complications of coronary heart disease, peripheral vascular disease, and stroke[2].

Most of the patients are initially managed with oral antidiabetic agents (OADs), while most of the patients require insulin analogs which can help for easing the transition to insulin therapy and often delayed until glycemic control has been inadequate for many years[3].

A constant increased prevalence of diabetes mellitus has changed the patterns of prescribing, recent studies reveal that only one third of the diabetics achieve glycemic control which require the physicians to re-evaluate the management options of this morbidity. Physicians are encouraged while identifying actively and addressing patients' concern regarding treatment modality[4].

Basically, functional decline in insulin-secreting beta-cells is responsible for uncontrolled glycemic levels.

The key target for long-term management strategies include preservation of β-cell functionality in addition to maintaining glycemic control and reduction of insulin resistance[5].

## MATERIAL & METHODS

In this study, we included 30 cases of type-2 DM uncontrolled on maximum doses of oral hypoglycemics with BMI in between 25 to 42, HbA1c in between 8% to 12%, fasting blood glucose> 126mg on screening from Department of Medicine, Services Hospital, Lahore were included in the study. Patients with Type-1 DM, accelerated hypertension, Age >64 years and <25 years, congestive heart failure (Class IV), prior use of agents affecting glycemic control like glucocorticoids, non-selective beta blockers, diuretics, weight loss drugs except orlistat, moderately severe impaired renal and hepatic function were excluded from the study.

Each patient was explained the purpose of the study and the likely benefits of the treatment. Every participant was requested to give written consent.

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Complete history and physical examination was done. Fasting and random blood sugar level and HbA1c was recorded. A single dose of intermediate acting insulin (NPH) was added at bed-time to uncontrolled diabetics already on maximum dose of oral hypoglycemia drugs. Starting dose of NPH was 12 units and titrated according to the fasting and random blood glucose level. Each patient was followed-up twice weekly for one week and then fortnightly for 3 months. The data was entered and analysed in SPSS 14.0. Descriptive statistics were calculated. The numerical variables of the study like age, duration of disease, dose of insulin fasting and random blood sugar levels. These variables were expressed as Mean±S.D. The qualitative variables like sex, and type of oral hypoglycemic drugs were presented as percentages. For comparison of blood sugar levels at the start of study and after three months paired sample "t" test was applied. P value <0.05 was taken as significant.

## RESULTS

The age ranged from 35-60 years with mean age being 46.0±7.9. Duration of diabetes in these patients ranged from 1-7 years, with mean duration being 4.1±1.8. Out of 30 patients, 17 patients (56.7%) had duration of diabetes 1-4 years while remaining 13 patients (43.3%) had duration of 5-7 years (Table 1). Sex distribution showed 15 male (50%) and 15 female (50%) (Table 2). The fasting blood sugar level showed decline with increasing dose of insulin over the period. Mean value of blood sugar fasting (baseline) was 161.97±13.94 which decreased to 100.80±.08.92, at 12$^{th}$week follow up. Results were statistically significant (P <0.001) (Table 3). The random blood sugar level showed decline with increasing dose of insulin over the period of 12 weeks. Mean value of blood sugar random (baseline) was 262.70±19.05 which decreased to 153.17± 28.14, at 12$^{th}$ week follow up. Results were statistically significant (P<0.001) (Table 4). The HbA1c levels at baseline and 12$^{th}$ week recorded as 9.20±40 and 7.13±0, respectively (Table 5).

Table 1: Distribution of patients by duration of diabetes (n=30)

| Duration (year) | n | %age |
|---|---|---|
| 1-4 | 17 | 56.7 |
| 5-7 | 13 | 43.3 |

Table 2: Distribution of patients by gender(n=30)

| Gender | n | %age |
|---|---|---|
| Male | 15 | 50 |
| Female | 15 | 50 |

Table 3: Comparison of blood sugar fasting (baseline) with blood sugar fasting (12th week)

| Blood sugar | Mean | SD |
|---|---|---|
| Fasting (baseline) | 161.97 | 13.94 |
| Fasting (12$^{th}$week) | 100.80 | 08.92 |

*P value 0.001*

Table 4: Comparison of blood sugar random (baseline) with blood sugar random (12th week)(n=30)

| Blood sugar | Mean | SD |
|---|---|---|
| Random (baseline) | 262.70 | 19.05 |
| Random(12$^{th}$week) | 153.17 | 24.14 |

*P value 0.001*

Table 5: Comparison of HbA1c (baseline) with HbA1c (12th week)(n=30)

| HbA1c | Mean | SD |
|---|---|---|
| Baseline | 9.20 | 0.40 |
| 12$^{th}$week | 7.13 | 0.22 |

*P value 0.001*

## DISCUSSION

There is little consensus regarding insulin therapy in type-2 diabetes, but intermediate acting insulin given at night has proved to be as effective as multi-dose insulin regimen without much weight gain. In current study, we added single dose insulin at bed time (intermediate NPH) to already uncontrolled type-2 diabetes on two oral hypoglycemic drugs and results were compared.

Yki-Jarvinen et al conducted a randomized control trial on 96 patients of type-2 diabetes to confirm bedtime insulin regimen in type-2 diabetes mellitus with uncontrolled sugar level to control fasting blood sugar level without much weight gain and hypoglycemia. The results were consistent with present study i.e. decreased HbA1c was seen with insulin and metformin 9.2±0.4 to 7.2±0.2, it was significant decrease (P<0.001) these results were similar to the present study in which HbA1c level decreased from 9.20±0.40 to 7.13±0.22 (P<0.001). It was associated with much less weight gain 3.6±0.7kg as compared to oral drugs alone 4.6±1.0kg[6].

Chow et al[7] evaluated the efficacy, side effects and quality of life on patients receiving insulin alone with those having combined insulin with oral anti-diabetic drug. Mean patients age was 53.9±12.6 years, mean duration of diabetes was 9.0±4.9 years and mean body mass index was found 24.21±4.3 Kg and half given insulin alone and other 23 patients given insulin in combination with oral hypoglycemic drugs with aim of fasting blood sugar level <7.8 upto 8 weeks. Insulin dose, body weight, glycemic control, quality of life at 3 and 6 month evaluated. The combination therapy decreased fasting blood sugar level (13.5±2.7 to 8.9±30) whereas 8.94 to 5.8 mmol/L, in my study. HbA1c decreased 10.2 to 8.4

and in my study it decreased from 9.2±0.40 to 7.13±0.22. Chow et al reported insulin requirement in combination is 14 units whereas when insulin is used alone 57 units were reported. In my study too, it was 14 units[7].

Landstedt-Hallin et al[8] showed that addition of bedtime NPH in secondary sulfonylurea failure showed decrease in fasting blood glucose of 6.4±3.0 mmol/L and HbA1c showed a decreased in level from 9.1±1.1 to 7.5±1.5 (P<0.001). These results comparable with findings of my study in which level of HbA1c decreased from 9.20±0.40 to 7.13±0.22 (P<0.001)[8].

Spellman[4] showed that early combining insulin in uncontrolled type-2 DM to maximum oral anti-diabetic drug was able to decrease HbA1c level. Together with these, he stressed upon nutritional therapy, physical activity and this was also able to improve complication like blood pressure and cholesterol[4].

Poulsen et al[9] reported that when baseline NPH to metformin, sulfonylurea and rosiglitazone in 16 obese type-2 diabetic decreased HbA1c from 8.8 to 6.8 mmol/L (P<0.001) without much hypoglycemia. In present study HbA1c decreased from 9.20±0.40 to 7.13±0.22 (P<0.001)[9].

Yki-Jarvinen[10] confirmed by finding of more than 6 mmol fall in fasting blood sugar level with combination therapy of insulin and oral hypoglycemic drug and fall of HbA1c maintain at level of 7.5 HbA1c as compared to 7.13 in my study[10].

DeFronzo[11] further confirmed combination therapy of bedtime insulin to oral hyperglycemic agent decreased basal rate of hepatic glucose production and decreased hypoglycemia by minimally stimulated the muscle uptake of glucose. He did this by 16 randomized studies where he compared placebo and insulin therapy to show decrease in fasting blood sugar level and HbA1c by 50-60% together with 50% less weight gain. This was evident by HbA1c fall of 2.5±0.4, weight gain of 0.9kg in 1 year as compared 3.6Kg with drugs alone, 4.6Kg weight gain of with insulin alone[11].

DeWitt and Hirsch[12] showed role of combining insulin to oral anti-diabetic drug on outdoor patient showed significant fall of HbA1c (P<0.05) and less hypoglycemia of (P<0.05). Most important was less weight gain of 0.9±0.01 (P<0.001) to 3.0±4.6 with oral anti-diabetic drugs only[12].

## CONCLUSION

Early addition or switch over of insulin to the already regime help achieve and maintain the goal glycemic control. The regime of combining bedtime insulin to oral hypoglycemic drug is not only effective in achieving and maintain the glycemic level, but also comes with less side effects like hypoglycemic and weight gain. Thus, delay and prevent the micro and macro vascular complication of diabetes.

## REFERENCES


1. Zimmet P. Diabetes epidemiology as a trigger to diabetes research. Diabetologia 1999;42:499-518.
2. American Diabetes Association, National Institute of diabetes and Digestive and Kidney Diseases. Prevention or delay of type 2 diabetes. Diabetes Care 2004;27:S47-S54.
3. Levy P. Insulin analogs or premixed insulin analogs in combination with oral agents for treatment of type 2 diabetes. MedGenMed 2007;9:12-4.
4. Spellman CW. Insulin therapy for maximal glycemic control in type 2 diabetes mellitus. J Am Osteopath Assoc 2007;107:260-9.
5. Hanefld M. Pioglitazone and sulfonylureas: effectively treating type 2 diabetes. Int J Clin Pract Suppl 2007;153:20-7.
6. Yki-Jarvinen H, Ryysy L, Nikkila K, Tulokas T, Vanamo R, Heikkila M. comparison of bedtime insulin regimens in patients with type 2 diabetes mellitus. A randomized, controlled trial. Ann Intern Med 1999;130:389-96.
7. Chow CC, Tsang LW, Sorensen JP, Cockram CS. Comparison of insulin with or without continuation of oral hypoglycemic agents in the treatment of secondary failure in NIDDM patients. Diabetes Care 1995;18:307-14.
8. Landstedt-Hallin L, Adamson U, Arner P, Bolinder J, Lins PE. Comparison of bedtime NPH or preprandial regular insulin combined with glibenclamide in secondary sulfonylurea failure. Daibetes Care 1995;18:1183-6.
9. Poulsen MK, Henriksen JE, Hother-Nielsen O, Beck-Nielsen H. the combined effect of triple therapy with rosiglitazone, metformin, and insulin aspart in type 2 diabetic patients. Diabetes care 2003;26:3273-9.
10. Yki-Jarvinen H. combination therapies with insulin in type-2 diabetes. Diabetes care 2001;24:758-67.
11. DeFronzo RA. Pharmacologic therapy for type 2 diabetes mellitus. Ann Intern Med 1999;131:281-303.
12. Edelman s, Dailey G, Flood T, Kuritzky L, Renda S. A practical approach for implementation of a basal-prandial insulin therapy regimen in patients with type 2 diabetes. Osteopath Med Prim Care 2007;1:9-1