ORIGINAL RESEARCH ARTICLE

Comparison of Metformin and Insulin Monotherapy with Combined Metformin and Insulin Therapy in Patients of Type 2 Diabetes with HbA1c > 7%.

Varsha Galani [1*], H. M. Patel[1]

[1*]Department of pharmacology, A. R. College of Pharmacy & G. H. Patel Institute of Pharmacy, Vallabh Vidyanagar-388120, Gujarat, India.

ABSTRACT

Early and intensive glycemic control is necessary to prevent or minimize the development of micro vascular and macro vascular complications in individuals with type 2 diabetes mellitus. In the present study, clinical efficacy of the metformin, insulin and metformin plus insulin was compared in the patients of type 2 diabetes mellitus with HbA1c > 7%. In an open-label, monocentric controlled trial, 45 patients of type 2 diabetes with HbA1c > 7% were randomly divided in to three groups (n=15). First group treated with metformin (1000 mg), second group treated with insulin (10 IU) and third group treated with insulin (10 IU) plus metformin (500 mg) for 3 months duration. Fasting blood glucose, postprandial blood glucose and HbA1c level were measured before treatment and after 3 months of each treatment course. Result of this study indicated that significant reduction in fasting and postprandial blood glucose level was observed in all treatment groups. Significant reduction in HbA1c level was also observed in all treated patients. Combined treatment of metformin and insulin caused 26% more reduction in HbA1c level than metformin and 11.41% more reduction than insulin monotherapy. In conclusion, therapy with insulin alone or with metformin in patients having poor glycemic control may be a useful and safe therapeutic approach in type 2 diabetes.

Key words: Glycosylated haemoglobin, Insulin, Type 2 diabetes mellitus, HbA1c

INTRODUCTION:

Type 2 diabetes mellitus is a complex disease characterized by insulin resistance and a progressive decline in β-cell function and mass. Current evidence suggests that β-cell dysfunction is present early in the course of the disease and this dysfunction, rather than insulin resistance is primarily responsible for the progression of type 2 diabetes mellitus.[1] Treatment of patients with type 2 diabetes often begins with monotherapy using an oral hypoglycemic agent from one of five classes: sulfonylureas, meglitinides, thiazolidinediones, biguanides, and α-glucosidase inhibitors. If glycemic control worsens, a second oral agent is usually added.[2] Studies show that after 3 years of treatment, approximately 50% of patients require more than one pharmacological agent,[3] and most patients with type 2 diabetes eventually require insulin.[4] Currently, 6 to 7 million Americans with diabetes (types 1 and 2)

use human insulin or insulin analogs (types 1 and 2);[4] approximately 30% of patients with type 2 diabetes receive insulin therapy.[5] Failure to achieve glycemic control may be partially due to the fact that oral therapy (e.g., sulfonylurea, metformin) does not appear to have a significant effect on progressively diminishing β-cell function,[6] although the thiazolidinedione class of insulin-sensitizing agents is under investigation as a diabetes-preventive agent.[7] By contrast, insulin therapy aimed at increasing basal insulin levels often ameliorates the effects of impaired β-cell function. Glycosylated hemoglobin (HbA1c) is considered the "gold standard" to evaluate the degree of glycemic control in patients with diabetes.[8] Based on ACE and ADA guidelines, physicians should consider initiating insulin therapy in patients with HbA1c concentrations greater than 7.0% despite treatment with oral agents.[4,8,9] In the UKPDS, mean blood glucose

*Corresponding Author: Varsha Galani, **Email:** vrp173@yahoo.com,

concentrations and HbAlc levels increased steadily, irrespective of treatment with diet, oral agents, or insulin and progressively required multiple therapy.[10] The use of metformin in combination with insulin has also demonstrated improved blood glucose control over insulin therapy alone. [11,12] However, a direct comparison of insulin and metformin monotherpy with insulin in combination with metformin has not been done. Based on this, present study was designed to compare efficacy of metformin, insulin and insulin plus metformin therapy in patient with glycosylated haemoglobin (HbA1c) level more than > 7%.

MATERIAL AND METHOD:

A study was carried out on 45 patients (of either sex) having type 2 diabetes attending Sarthi Medical and Diabetes Hospital, Anand, Gujarat, India. All the patients have reported glycosylated haemoglobin more than 7% (HbA1c > 7%) with routine oral hypoglycemic agents treatment. Patients of history of cancer and/or drug abuse, actual or intended pregnancy, breastfeeding, major pathology affecting the liver, kidney, cardiovascular/central nervous systems, and known hypersensitivity to insulin were excluded from the study. Patient's consents were taken before including them into the study. All 45 patients for the study was randomly selected and divided them in to 3 groups by taking alternate patient in each group (n=15). Group 1 was treated with metformin (1000 mg), group 2 was treated with isophane insulin (10 IU once daily) and group 3 was treated with combination of isophane insulin (10 IU once daily) and metformin (500 mg) therapy. Detailed history of the patients was taken with special reference to history of drug intake and allergy before initiating therapy. Investigation of glycosylated haemoglobin (HbA1c), fasting blood sugar (FBS) and postprandial blood sugar level (PP2BS) was carried out before and after 3 months of each treatment course.

Statistical analysis

Data were expressed as mean ± S.E.M. The statistical significance of difference between groups was evaluated by one-way analysis of variance (ANOVA). Paired student's t test was performed for comparison of before and after treatment data. A probability level of 0.05 or less was accepted as significant.

RESULTS:

A total of 45 subjects were randomized in to three groups each group containing 15 patients. They received study treatment metformin, insulin and insulin plus metformin respectively. There were no significant differences between groups with regard to demographics and diabetic disease characteristics (**Table 1**). Result of effect of metformin, insulin and insulin plus metformin treatments on fasting blood sugar level of patients are shown in (**Figure 1**). Treatment with metformin was produced 8 % reduction in the levels of fasting blood sugar level (114.20 ± 2.47 vs 105.07 ± 2.15, p < 0.05). Treatment with insulin led to 16.10 % reduction (130.40 ± 3.69 vs 109.40 ± 2.65, p < 0.05) in the levels of fasting blood sugar level. Treatment with insulin plus metformin was more effective in achieving glycemic control, as it led to 35 % reduction (174.47 ± 5.89 vs 113.40 ± 2.59, p < 0.05) in the levels of fasting blood sugar level.

Result of effect of drug treatments on postprandial blood sugar level is shown in figure 2. As shown in (**Figure 2**), treatment with metformin led to 8.57 % reduction (188.93 ± 5.35 vs 172.73 ± 4.20, p < 0.05) in the levels of postprandial blood sugar level. Treatment with insulin was also effective in achieving glycemic control, as it led to 30.83 % reduction (256.87 ± 8.82 vs 177.67 ± 5.11, p < 0.05) in the levels of postprandial blood sugar level. Combination therapy of insulin and metformin was more effective as compared to insulin and metformin alone as it led to 49.85 % reduction (352.53 ± 15.75 vs 176.80 ± 4.60, p < 0.05) in the levels of post prandial blood sugar level.

Result of glycosylated haemoglobin of metformin, insulin and insulin plus metformin treated groups is shown in (**Figure 3**). There was 9.40 % reduction in the levels of HbA1c was observed with metformin treatment (7.94 ± 0.16 vs 7.19 ± 0.13, p<0.05). Treatment with Insulin was also caused 23.99 % decrease in the levels of HbA1c (9.56 ± 0.19 vs 7.27 ± 0.16, p<0.05). Treatment with combination of insulin and metformin was produced more effective as it produced 35.40% reduction in the levels of HbA1c (10.77 ± 0.19 vs 6.96 ± 0.15, p<0.05).

Baseline characteristics of the treated patients			
	Metformin	Isophane insulin treatment	Isophane Insulin plus Metformin
Mean age (years)	54.60	61.40	55.20
Male: Female ratio	10:5	10:5	9:6
Mean weight (kg)	60.13	65.40	65.13
Mean pulse rate (per minute)	78.87	76.73	77.13
Mean systolic pressure (mmHg)	135.67	136.40	136.93
Mean diastolic pressure (mmHg)	80.73	79.80	80.67
Family history of diabetes (%)	86.66 %	86.66 %	86.66 %

Table 1. Baseline characteristic data of the type 2 diabetic patients treated with metformin, insulin and insulin plus metformin therapy.
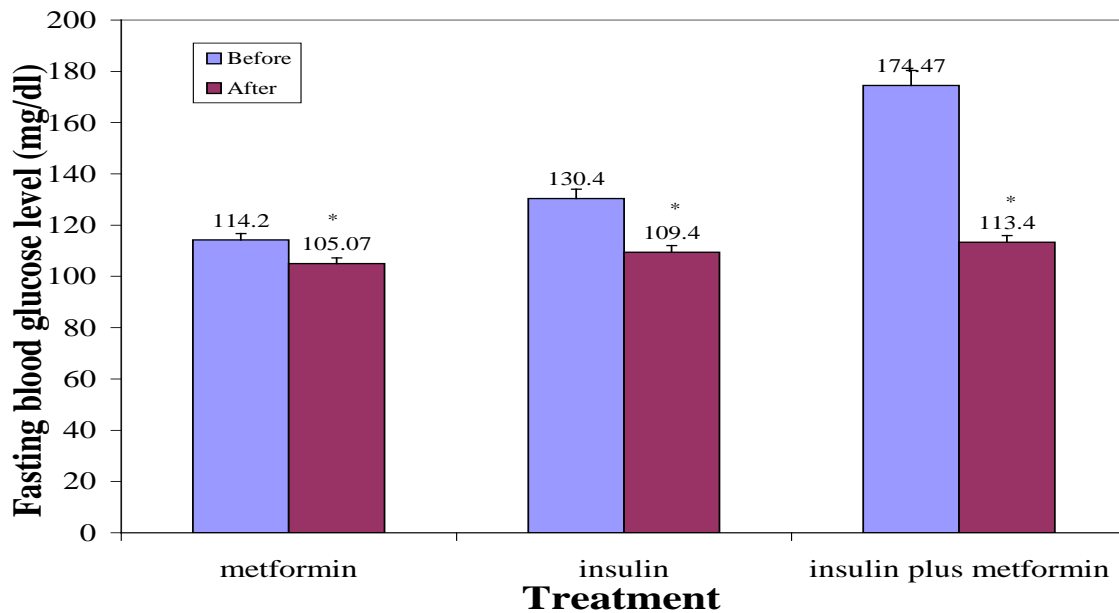
Figure 1. Effect of metformin, insulin and insulin plus metformin treatment on fasting blood sugar(FBS) level of type 2 diabetic patients. Each bar represents the mean ± S.E.M (n=15) One way ANOVA (Analysis of variance), Paired sample t-test $^{*}P<0.05$ when compared with before treatment FBS level.
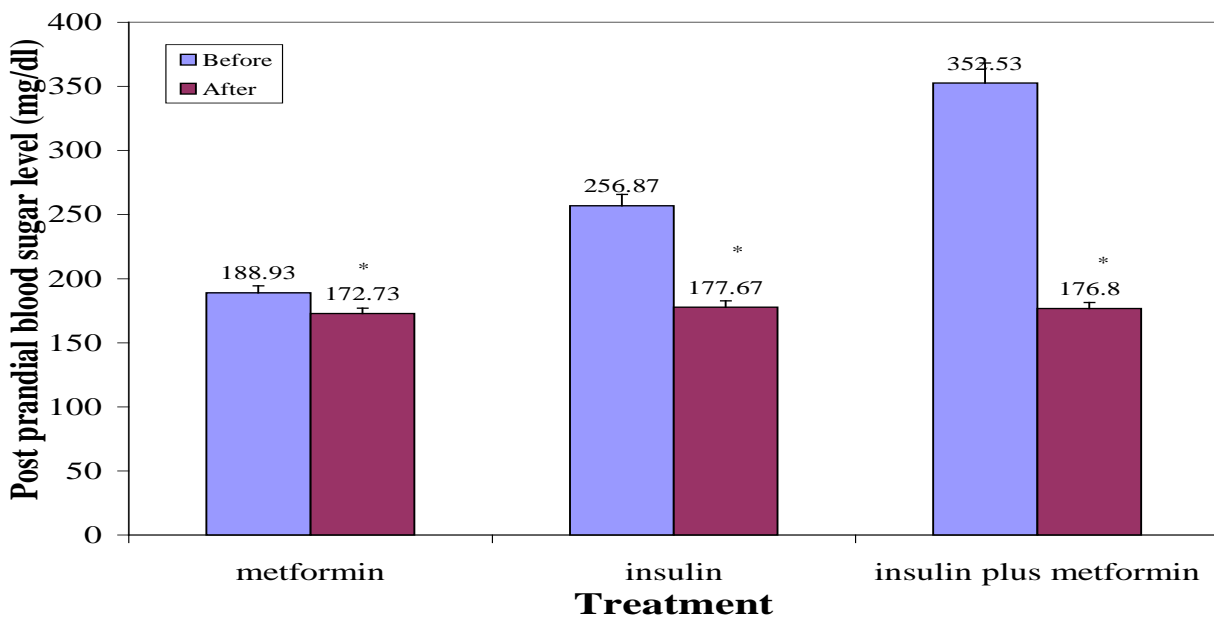

Figure 2. Effect of metformin, insulin, insulin plus metformin treatment on postprandial blood sugar(PP2BS) level of type 2 diabetic patients. Each bar represents the mean ± S.E.M (n=15) One way ANOVA (Analysis of variance), Paired sample t-test $^{*}P<0.05$ when compared with before treatment PP2BS level.
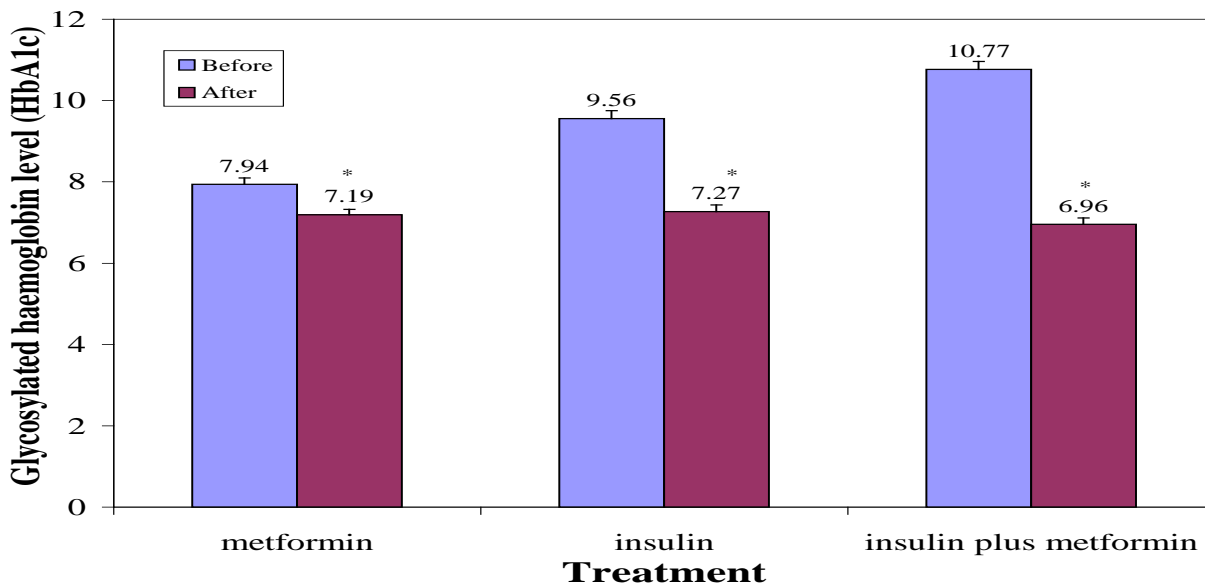
Figure 3: Effect of metformin, insulin, insulin plus metformin treatment on glycosylated haemoglobin(HbA1c) level of type 2 diabetic patients. Each bar represents the mean ± S.E.M (n=15) One way ANOVA (Analysis of variance) followed by paired t-test *P<0.05 when compared with before HbA1c level.

DISCUSSION:

Type 2 diabetes mellitus is a chronic metabolic disorder that results from defects in both insulin secretion and insulin action. An elevated rate of basal hepatic glucose production in the presence of hyperinsulinemia is the primary cause of fasting hyperglycemia; after a meal, impaired suppression of hepatic glucose production by insulin and decreased insulin-mediated glucose uptake by muscle contribute almost equally to postprandial hyperglycemia.[13] Fasting plasma glucose and postprandial plasma glucose values provide snapshots of basal glucose metabolism (i.e., hepatic glucose production) and, most importantly, exposure to postprandial glucose excursions, which have recently been linked to overall vascular damage.[1] HbA1c values reflect glycemic exposure during a period of ~ 3 months. The expected A1C value for people with normal glucose metabolism is 4.0-6.0 %. Recommended target values for individuals with diabetes are < 7%. Therefore, fasting blood sugar level, post prandial blood sugar level and glycosylated haemoglobin are the three laboratory measures recommended to gauge the level of glycemic control attained by individual patients.[8] Both acute and prolonged hyperglycemia adversely affects beta cell function[14] and this glucotoxicity leads to impaired gene transcription, down regulation of glucose transporters and alteration of transporter function induced by oxidative stress.[15]

Early and intensive glycemic control is necessary to prevent or minimize the development of microvascular and macrovascular complications in individuals with type 2 diabetes mellitus.[16] The current paradigm of management of type-2 diabetes is one of sequential addition of treatment modalities starting from medical nutrition therapy, exercise, single or combination oral hypoglycemic agents and finally insulin administration with or without oral hypoglycemics.[17] This strategy has miserably failed in achieving recommended glycemic goals to prevent microvascular as well as macrovascular complications. Patients with type 2 diabetes mellitus who still secrete endogenous insulin often do well receiving oral agents. The choice of oral agent depends largely on adverse effects and cost.[18] Metformin has become a cornerstone of therapy based on its efficacy, low risk of hypoglycemia, low risk of weight gain, and generic availability. The ADA/EASD treatment algorithm recommends its use, along with lifestyle modification, as the initial therapeutic strategy for patients with type 2 diabetes mellitus.[17] Over time, most patients with type 2 diabetes experience progressive β-cell dysfunction and will require insulin therapy, either alone or in combination with oral agents for satisfactory glycemic control.[19] Exogenous insulin does not increase the risk of macrovascular disease or exacerbate insulin resistance.[20] Insulin therapy also is indicated in patients with contraindications to antidiabetic medications.[21]

Intensive insulin therapy was found to reduce morbidity and mortality in critically ill patients in a surgical intensive care unit compared with usual therapy.[22] In patients who had experienced a myocardial infarct, intensive insulin therapy resulted in a 30 percent lower risk of death compared with usual therapy.[23] Many patients regain beta cell function after a few weeks of intensive therapy, enabling them to return to management with diet or oral medication for several months to years.[24]

Augmentation therapy is effective in patients with residual but insufficient beta-cell function, which is exhibited as failure to maintain the HbA1c goal while taking oral medications.[21] Weight gain is a common side effect of insulin therapy. Adding bedtime insulin, usually NPH, to oral agents is the standard approach to starting insulin therapy. Although insulin may be added to any approved oral agent, metformin does not cause weight gain and may offer additional cardioprotection[25] and thus is our first choice for use with insulin in patients without contraindications. Benefits of the combination of metformin and insulin include improved glycemic control, less weight gain, fewer episodes of hypoglycemia.[26,27] Metformin does not need dose adjustments when administered with insulin. Some available clinical reports also support our results that combined therapy of metformin and insulin is more effective than insulin therapy alone.[28,29] Patients randomized to insulin NPH plus metformin achieved similar A1C levels, fasting plasma glucose levels, and weight gain but had lower daily costs and treatment failures than patients randomized to triple oral medication (a sulfonylurea, metformin, and a thiazolidinedione).[30]

CONCLUSION:

An HbA1c level less than 7% consistently reduces microvascular complications and is now the goal for most patients. The timely addition of insulin to oral therapy in patients with this disease will generally lead to better outcomes than are obtained with traditional treatment approaches. In conclusion, therapy with insulin alone or with metformin in patients having poor glycemic control may be a useful and safe therapeutic approach in type 2 diabetes. Although, matching disease pathophysiology and patient-specific characteristics to therapeutic choices can improve treatment success for patients with type 2 diabetes mellitus.

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