JAOA

ORIGINAL CONTRIBUTION

Efficacy of combination therapy with insulin and oral hypoglycemic agents in patients with type II diabetes during a 1-year period

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In this retrospective study, the authors assess the efficacy of combined insulin and oral hypoglycemic agents (OHAs) in controlling glycemic levels, as well as lipid levels and insulin requirements, in 48 patients with type II diabetes mellitus during a 1-year period. Thirty-two of these patients had secondary failure to an OHA (group 1). Sixteen patients (group 2) were taking high doses of insulin alone. Overall, 64.6% of all the patients responded to the combination therapy and insulin at 6 months. Response was defined as a decrease in hemoglobin A_{1c} of more than 0.5%. At 12 months, 50% of these patients continued to respond to this regimen. No significant differences were seen in the patients' total cholesterol and triglyceride levels between responders and nonresponders in each group. After 1 year of combination OHA and insulin therapy, 50% of the patients showed a 21.4% reduction in their daily insulin dose.

(Key words: Type II diabetes mellitus, oral hypoglycemic agents, glucose control, insulin therapy)

With the increasing concern over the role of hyperinsulinemia in the development of hypertension,[1] atherosclerosis,[2,3] and dyslipidemia, the aim to decrease the dose of exogenous insulin by prescribing a combination of an oral hypoglycemic agent (OHA) and insulin seems logical. Similarly, combining insulin with an OHA may provide an alternative means to manage patients with type II diabetes mellitus who previously failed to maintain good glycemic control with insulin or OHA therapy alone.

In the early course of the disease, many patients with type II diabetes mellitus (C-peptide reactive) have hyperinsulinemia develop as a result of insulin resistance. These patients may benefit from combination OHA and insulin therapy rather than from increased doses of exogenous insulin.

The purpose of this study was to assess the effect of prolonged insulin and OHA therapy combined during a 1-year period on glycemic control, lipid profile, and insulin requirements of patients with type II diabetes mellitus.

Materials and methods

A retrospective assessment was made regarding the efficacy of insulin therapy combined with an OHA in 48 patients with type II diabetes mellitus (C-peptide reactive) in an outpatient clinic setting. Record analysis found that of these patients, 32 had had prior failure to an OHA: glipizide (19 patients), glyburide (5 patients), chlorpropamide (6 patients), tolbutamide (1 patient), tolazamide (1 patient). Insulin (mean dosage, 27.4 units/kg per day) was added to their regimen (group 1). Patients in group 1 were maintained on the same dose of their original OHA. The efficacy of individual OHAs was not ascertained.

Sixteen patients who had difficulty maintaining their glucose levels despite being on a high dose of insulin alone (mean dosage, 0.87 units/kg per day) had glipizide (mean dosage, 10 mg) added to their insulin therapy (group 2).

All patients were followed up in the outpatient clinic every 3 months. Changes were made in insulin and OHA dosages based on the patient's glycosylated hemoglobin (HbA_{1c}) levels and results from home monitoring of capillary blood sugar levels. Data were analyzed for the patients' HbA_{1c}

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Table 1
Variables Among Responders and Nonresponders on Combined Therapy

Variable	Responders (N=24)	Nonresponders (N=24)	*P* value
Men, No.	9	10	.763
Women, No.	15	14	1.000
Age, y	61.0±12.8*	53.9±10.6*	.023
Duration, y	10.0±12.8	10.9±8.0	.399
HbA_{1c}	10.0±1.6	8.2±1.8	<.001
C-peptide	3.7±2.1	3.3±2.1	.286
Cholesterol, mg/dL	242±86	246±58	.437
Triglycerides, mg/dL	262±181	253±150	.437
Body mass index	31.8±31.8	31.6±31.6	.457

*All subsequent values are mean ± SD.

of variation for the HbA_{1c} assay in our laboratory was 3%.

Patients whose HbA_{1c} levels did not fall within the prescribed parameter were classified as nonresponders.

Blood was drawn at the time of outpatient visits to measure each patient's fasting HbA_{1c} levels and lipid profile. The HbA_{1c} was measured using the Hemoglobin A1c Micro Column Test (Bio Rad Diagnostics Group, Hercules, Calif). The C-peptide levels were measured using the polyethylene glycol (PEG) method (RIA) (Serono Diagnostics, Inc, Allentown, Pa). Total cholesterol was measured using the CAP Comprehensive Chemistry Survey 903 Hitachi 717/089 Enzymatic (Boehringer Mannheim Corp, Indianapolis, Ind). Triglycerides were measured using the CAP Comprehensive Chemistry Survey 903 Hitachi 717/227 Enzymatic–Colorimetric (Boehringer Mannheim Corp, Indianapolis, Ind).

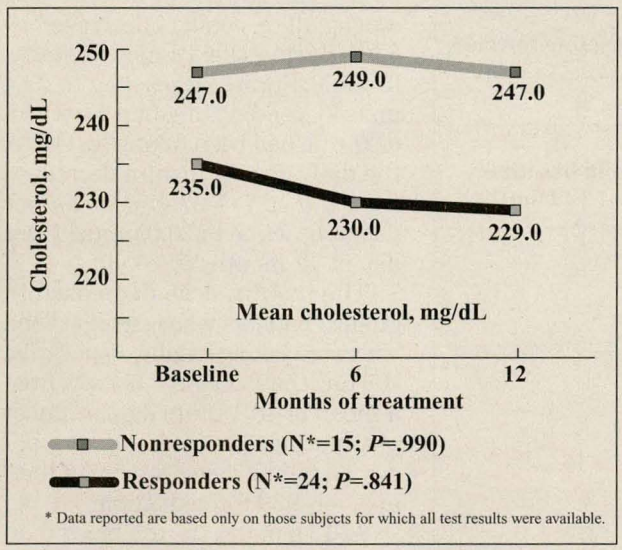

Figure 1 (top). *Cholesterol changes in responders and nonresponders on insulin-OHA combined therapy at baseline to 12 months.*

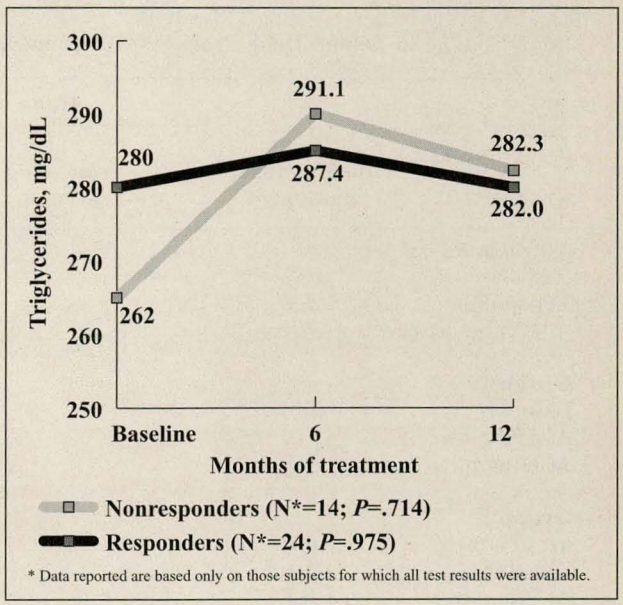

Figure 2 (right). *Comparison of triglyceride levels in responders and nonresponders on insulin-OHA combined therapy at baseline to 12 months.*

levels, lipid profiles, and insulin requirements at baseline, 6 months, and 12 months.

Group 1 included 15 male and 17 female patients. Group 2 comprised 4 male and 12 female patients. Mean age for both groups was 57.5 years. The mean duration of known type II diabetes mellitus was 10.0 years. Based on statistical calculation, a response to therapy was defined as a decrease in HbA_{1c} of more than 0.5%. The coefficient

Statistical methods

All results are reported as a mean ± 1 standard deviation (SD). Comparison of baseline characteristics for responders and nonresponders was ascertained using the Student *t*-test for unpaired data. Repeated measures analysis of variance (ANOVA), followed by Tukey's test, was used to detect and to isolate differences in selected variables during the 12-month study period. All tests were two-

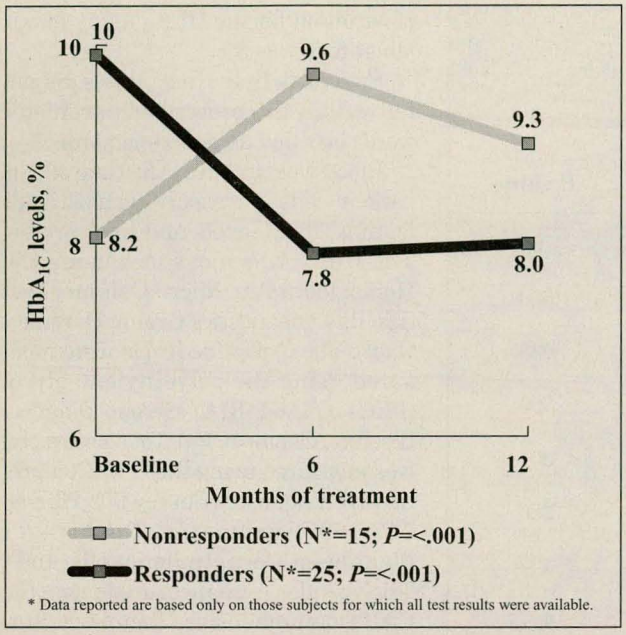

Figure 3. *Changes in HbA_{1c} levels in responders and nonresponders in insulin-OHA combined therapy at baseline to 12 months.*

Table 2
Mean Change in Insulin Dose From Pretreatment and Baseline Levels

Group	Mean insulin dose, units/kg/d	Mean change, %	
		From pretreatment	From baseline at 12 months
All responders			
Baseline	29.3		
At 6 months	22.8		
At 12 months	27.4		−6.7
Group 1			
Baseline	27.4		
At 6 months	25.0		
At 12 months	23.0		−15.7
Group 2			
Pretreatment	48.1		
Baseline	29.0		
At 6 months	31.6		
At 12 months	37.9	−21.4	+30.5

tailed with the type 1 error set at $P < .05$.

Results

Of the 48 study participants in both groups, 31 (64.58%) were classified as responders at 6 months. Responders were defined as having at least a 0.5% decrease in their HbA_{1c} levels. At 12 months, 24 patients (50%) remained classified as responders.

Specifically, group 1 was composed of 24 (75%) responders and 8 (25%) nonresponders, while group 2 had 7 (43.75%) responders and 9 (56.25%) nonresponders at 6 months. In both groups, no difference was found in response to therapy at 12 months.

Comparison of insulin dosage at pretreatment and baseline with that at 12 months (*Table 1*) revealed no significant differences between responders and nonresponders regarding: duration of type II diabetes mellitus, C-peptide levels, total cholesterol and triglyceride levels, and body mass index (BMI). However, compared with nonresponders, responders were significantly older ($P = .023$) and had higher baseline HbA_{1c} values ($P < .001$). Compared with baseline values, no statistically significant difference was seen in the total cholesterol and triglyceride values at 12 months for the overall study population.

Similarly, no statistically significant difference was seen when the total cholesterol and triglyceride values for responders and nonresponders were compared at baseline, 6 months, and 12 months (*Figures 1* and *2*). The HbA_{1c} level did decline significantly among responders, while increasing significantly among nonresponders at 6 months. Thereafter, however, it remained unchanged in both groups between the 6th and 12th months (*Figure 3*).

Overall, the mean insulin dose among all responders decreased by 6.7% during the 12-month study: from 29.3 units/kg per day to 27.4 units/kg per day. In group 1 (responders who had been taking an OHA), the daily dose of insulin decreased from a mean of 27.4 units/kg per day at baseline to 23.0 units/kg per day at 12 months.

The insulin dose decreased in group 2 patients who responded and who were taking insulin alone *before* starting the combined therapy: from a mean of 48.1 units/kg per day at pretreatment to 29.0 units/kg per day on commencing combined therapy, for a 39.8% reduction.

At 12 months, the combined therapy caused a decline in the mean insulin dose, from a pretreatment level of 48.1 units/kg per day to 37.9 units/kg per day, a 21.4% reduction (*Table 2*).

Overall, the average absolute decrease in the HbA_{1c} levels among all responders was 2.2% at 6 months; at 12 months they decreased to 2.0% (*Table 3*). Among responders in group 1, the decrease in HbA_{1c} measured 2.2% at 6 months and 2.5% at 12 months. A slight decline in HbA_{1c} was noted among group 2 responders, from 1.3% at 6 months to 1.2% at 12 months.

Figure 4 shows the relationship of insulin dosage to

Table 3 Average Absolute Decrease in HbA_{1c} Values in Responders		
	At 6 months (%)	At 12 months (%)
All responders	2.2	2.0
Group 1	2.2	2.5
Group 2	1.3	1.2

body mass index among responders in both groups.

Discussion

Diabetes is a disorder characterized by abnormal insulin secretion by the pancreatic B cells, as well as an increase in peripheral resistance to insulin action. Although insulin levels may vary during the course of the disease, they remain inadequate to ensure normoglycemia. In a fed state, the patient has a decrease and delay in insulin secretion. Accompanying this is a decrease in glucose clearance that results in postprandial hyperglycemia. In the fasting state, an increase in the hepatic production of glucose occurs that is primarily responsible for the fasting hyperglycemia. Persistent hyperglycemia per se is toxic to the pancreatic B cells, and a progressive decline in insulin secretion has been observed with increased fasting blood glucose levels. Finally, in the presence of marked fasting hyperglycemia (> 180 mg/dL), the plasma insulin response becomes flat. In addition, in type II diabetes, a postreceptor defect inhibits the transportation of glucose into cells, thereby leading to hyperglycemia and hyperinsulinemia. The high insulin levels cause downregulation of insulin receptors, and the vicious cycle continues.

Sulfonylureas stimulate release of insulin by B cells by binding to specific high-affinity sulfonylurea receptors. The duration of this effect varies with different OHAs. For example, with glyburide, the effect lasts 5 to 9 months, while the effects of glipizide persist 9 to 12 months. In vitro and in vivo evidence suggests that sulfonylureas potentiate the action of insulin in both peripheral and hepatic tissues, and this action is not a result of enhanced insulin levels or binding. Rather, it occurs at a site distal to where insulin binds to its plasma membrane receptor.

The results of the recently concluded Diabetes Control and Complications Trial (DCCT)[4] emphasize the importance of achieving near-normal control of blood glucose in preventing or delaying (or both) primary and secondary complications in type I diabetes mellitus. The same may apply to type II diabetes mellitus. Most diabetics have type II diabetes mellitus. Of these, 20% to 30% have a primary failure to sulfonylureas. An additional 5% to 10% of these patients have secondary failure each year. In some of these patients, combination therapy (insulin and sulfonylureas) is a reasonable option.

The rationale for using combination therapy is twofold: Sulfonylureas improve diabetic control through

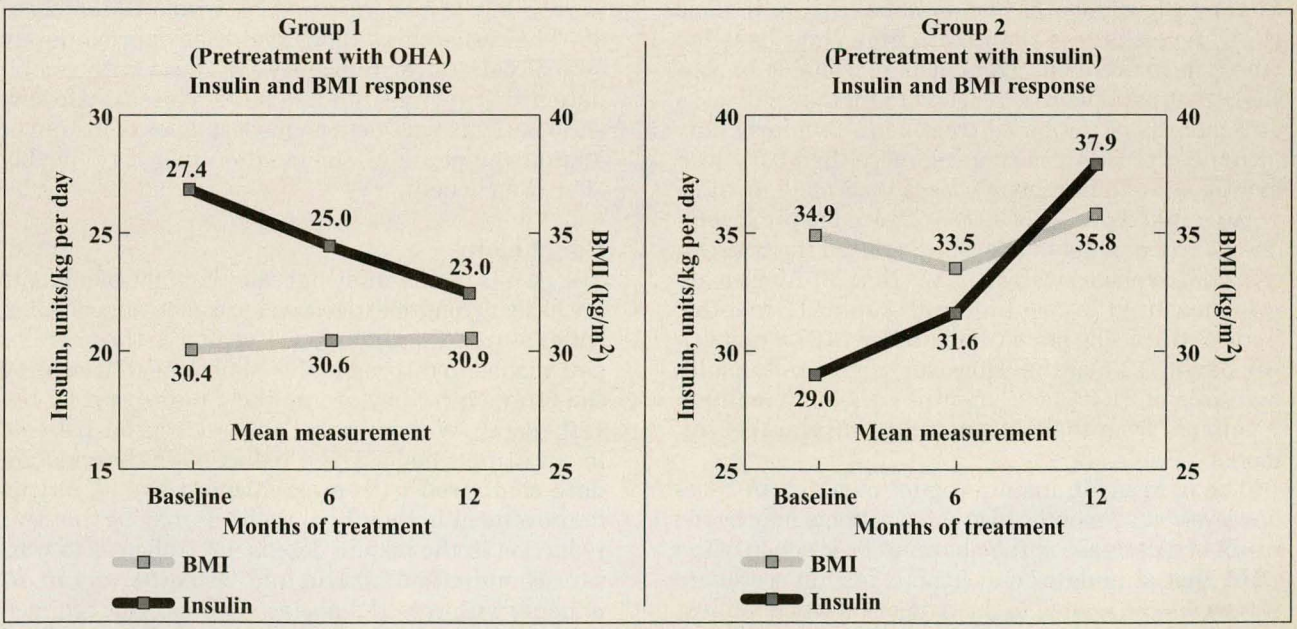

Figure 4. Changes in insulin and body mass index (BMI) among group 1 and group 2 subjects on insulin-OHA combined therapy at baseline to 12 months.

their pancreatic and extrapancreatic effects. They may also decrease the need for exogenous insulin and thus prevent the peripheral hyperinsulinemia. As hyperinsulinemia may have a role in promoting atherosclerosis, preventing hyperinsulinemia may be an added benefit of combination therapy.

The purpose of this study was to evaluate the efficacy of combination insulin and OHA therapy in patients with type II diabetes mellitus in an outpatient clinic. Numerous studies have compared the effectiveness of such therapy in such a patient population, but no uniform criteria had been established to define improvement in or deterioration of glycemic control. There has been a lack of consistency in the results reported, with some studies showing significant improvement in glycemic control,[5-16] while others have failed to show any improvement.[17-19] Even in studies that showed no improvement, no deterioration in glycemic control was found either. Most of the reported results were based on duration of 4 weeks to 6 months and had a small patient population (range, 5 to 25 patients).

In the study reported here, combination therapy worked in both groups. Patients with secondary failure to an OHA were more likely to respond to the addition of insulin to their regimen than the patients with type II diabetes mellitus who were already taking large doses of insulin and who had an OHA added to their regimen. After 1 year, the average absolute decrease of the HbA_{1c} level in group 1 was 2.5% and 1.2% in group 2.

Interestingly, all the patients in both groups who had an increase of more than 0.5% in their HbA_{1c} level at 6 months failed to respond at 12 months. Those few patients who *did* respond to the combined therapy after 6 months had an initial change in their HbA_{1c} levels of less than 0.5% from their baseline HbA_{1c} measurement. Thus, it is reasonable to conclude that patients who respond to therapy will do so at 6 months of combined treatment. Similarly, any increment of HbA_{1c} measuring more than 0.5% at 6 months is an indication of *nonresponse* at 12 months.

An initial decrease of 39.8% occurred in the insulin dosage when patients in group 2 started the regimen of insulin combined with an OHA (*Table 2*). An increase was measured in insulin dosage up to 12 months, from 29.0 units/kg per day at baseline to 37.9 units/kg per day at 12 months. However, an overall insulin *reduction* of 21.4% at 12 months was found in group 2 patients from their pretreatment insulin requirements.

The increase in insulin requirements from baseline levels at 12 months in group 2 patients may be the result of a decrease in the pharmacologic action of the OHA that stimulates endogenous insulin secretion. It may also be related to the patients' waning interest and dietary compliance after 6 months of therapy.

An improvement in glycemic control did occur, which may be because of improved insulin action. Even in group 1, patients who continued to respond at 12 months had a 15.7% reduction in the insulin dose from that prescribed at baseline (*Table 2*). Other studies[8,17,18,20,21] have found a 10% to 40% reduction in insulin dose in patients on combined insulin-OHA therapy.

No significant changes in lipid profiles were seen in the responders or nonresponders at 12 months (*Figures 1* and *2*). This finding concurs with results from other studies.[15,21-23] A reduction in serum triglyceride levels has been reported by some investigators.[17,21,24] In our study, we hypothesize that the change in the HbA_{1c} levels in the responders may not be large enough to influence any changes in the lipid profile or that any lipid changes may be independent of glucose control.

We also analyzed the patients' pretreatment characteristics (*Table 1*) to determine if it was possible to predict the type of patients most likely to respond to combined therapy. No significant difference was seen between the responders and nonresponders in duration of diabetes, baseline C-peptide values, cholesterol and triglyceride levels, and BMI. However, a significant difference was found in the older patients (mean age, 61 years) who classified as responders. Responders from both groups were also found to have a higher initial level of HbA_{1c} than nonresponders. Other studies[15,25] found responders to have higher fasting C-peptide values,[25,26] greater BMI,[12,15,25] and a shorter duration of disease than nonresponders.[8]

Reaven and colleagues[13] found no differences among responders with regard to HbA_{1c} levels, age, sex, BMI, or daily insulin dose. Lebovitz and Pasmantier[27] reported that responders had poor initial glycemic control and were mildly to moderately obese, with a BMI of 25 to 35. The researchers concluded that approximately 30% of patients significantly improved with combination therapy (insulin and sulfonylureas). However, in patients who were on modest doses of insulin (< 40 units/kg per day), combination therapy probably offered no benefit.

Conclusion

The results of this study indicate that 50% of patients are likely to continue to respond to combination insulin-sulfonylurea therapy after 1 year. Furthermore, if patients fail to respond to this combination therapy by the 6th month, they are unlikely to respond by the 12th month. With improved glycemic control, patients in our sample had a 21.4% reduction in their insulin dose compared with pretreatment levels, but no improvement in their lipd profile. It may be that this reduction in the insulin dose is not sufficient to warrant combination insulin and OHA therapy in *all* patients with type II diabetes mellitus. This regimen exposes patients to the cumulative adverse effects associated with OHA and insulin, such as hypoglycemia,

gastrointestinal disturbances, and cholestasis. The substantial increase in the cost of this regimen may also prohibit it from being prescribed for all patients with type II diabetes mellitus.

Rather, an older patient (older than 60 years) with type II diabetes mellitus and poor glycemic control who is already taking an OHA alone will more likely respond to the combination insulin and OHA therapy. We think that such combination therapy may be considered for transitional therapy. If after 6 months patients fail to respond to this regimen, they will need to be treated with insulin alone. During this transitional phase, attempts should be made to foster dietary compliance and to encourage regular exercise so as to increase the likelihood that insulin will no longer be required.

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