# Effects of insulin-oral hypoglycemic agents combined therapy in outpatients with type 2 diabetes

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**Abstract.** – To evaluate the efficacy of combined insulin-OHAs therapy in subjects with NIDDM who received treatment with OHAs and insulin alone, we selected 60 outpatients divided in two groups:

*Group A:* 36 subjects treated with OHAs therapy that received insulin treatment for secondary failure; *Group B:* 24 subjects in which OHAs therapy was added to insulin regimen to avoid the effects of hyperinsulinization.

In the group A body weight increased significantly (+1.94 ± 2.80 kg, p< 0.001 vs baseline), while in group B no gain of body weight was observed. Both groups showed a similar improvement of glycemic control. For the group A, the FPG and HbA1c decreased, respectively, from 14.64 ± 3.76 to 8.72 ± 2.92 mmol/l and from 9.10 ± 0.30 to 7.20 ± 0.53% at 6 months (p< 0.001). For the group B FPG and HbA1c decreased, respectively, from 12.05 ± 3.49 to 8.24 ± 3.01 mmol/l and from 8.3 ± 0.1 to 6.8 ± 0.13% (p< 0.001). Plasma cholesterol, triglycerides and uric acid concentrations did not show significant changes in either group. Insulin requirement in group A was 0.21 ± 0.13 U/Kg/day. Despite of improvement of glycemia, total insulin requirement decreased in Group B from 0.53 ± 0.25 to 0.34 ± 0.2 U/Kg/day after OHAs therapy (p< 0.001). In the group A the bedtime insulin administration was prevalent (52.68%), while the most patients of group B needed a second or a third daily insulin injection (83.33%). In conclusion, in type 2 diabetic patients, therapy with combination of OHAs and insulin was associated with lower insulin doses and less weight gain.

Key Words:

Type 2 diabetes mellitus, Insulin-OHAs combined therapy.

## Introduction

Type 2 diabetes may be looked upon as a progressive disease where glycemic control gradually deteriorates with time. Thus, these patients are usually treated with OHAs when diet thera py alone fails to normalize glucose metabolism[1]. For patients not achieving an adequate control with such therapy, insulin treatment is the available option[2,3]. A recent meta-analysis concluded that combined insulin-OHAs therapy achieves similar glycemic control at a lower insulin doses when compared with insulin therapy alone[4]. Combined therapy may be considered also, in type 2 diabetes, when in subjects who received insulin therapy alone for intercurrent illness, OHAs were added. Potential benefits include less dose of insulin needed, less weight gain and less peripheral hyperinsulinemia[5].

In the present study, we evaluated the effects of combined insulin-OHAs therapy in subjects with type 2 diabetes who received treatment with OHAs and insulin alone. The study was performed in an outpatient setting, and the different therapeutical regimens were compared during a 6 months period.

## Materials and Methods

Among 900 clinical records of type 2 diabetic outpatients attending our University Clinic, 199 (22.11%) receiving insulin-OHAs combined therapy were recruited: of these 130 come from OHAs, 69 from insulin alone. We examined only the clinical records of patients in which were possible to identify the cross-over point to combined treatment and to follow them along six months of observation (no. 60), and selected two groups (Table I):

Table I. Baseline characteristics of study subjects before combined therapy.

|  | Group A | Group B | p |
|---|---|---|---|
| N | 36 | 24 |  |
| Sex (M/F) | 15/21 | 8/16 |  |
| Age (years) | 60.61 ± 10.59 | 60.91 ± 10.25 | n.s. |
| Duration of diabetes (years) | 12.69 ± 6.71 | 14.05 ± 8.21 | n.s. |
| BMI (kg/m²) | 27.22 ± 6.02 | 30.24 ± 4.01 | 0.035 |

Data are means ± SD.

*Group A:* 36 subjects treated with OHAs therapy that received insulin treatment for secondary failure;

*Group B:* 24 subjects in which OHAs therapy was added to insulin regimen to avoid the effects of hyperinsulinization. Both groups were omogeneous for age and median time since diagnosis of diabetes, while BMI at the admission was significantly lower in group A than in group B. All the patients received a standard diet, with total calories in relation to body weight, containing the same percent of carbohydrates (55-60%), lipids (20-25%) and proteins (15-20%). Meals were taken as follows: breakfast at 08.00 AM, lunch at 01.00 PM, dinner at 08.00 PM and two or three snacks at 11.00 AM, 05.00 PM and/or 11.00 PM. The patients of group A received maximum doses of glibenclamide or gliclazide with or without metformin (0.5-2 g/day) at baseline. We consider 15 mg/day to be the maximum dose of glibenclamide or 240 mg/day of gliclazide according to European experience[6].

The group B patients received similar doses of OHAs at the end of the stabilization period (6 months). Insulin treatment was added in group A, and modified in group B, in order to reach an adequate metabolic control. At baseline and after 6 months (treatment period after stabilization), body weight and insulin requirement were evaluated; moreover, fasting plasma glucose (FPG), glycosylated haemoglobin (HbA$_{1c}$), cholesterol, triglycerides and uric acid were considered.

Statistical analysis

Comparison between groups at baseline were performed by unpaired Student's t test. Responses to treatments were compared by Student's t test for paired data. All tests were two-tailed, with p< 0.05 considered significant. Results are presented as mean ± SD.

## Results

Tables II and III show the clinical and metabolic patterns as well as the insulin requirements and daily insulin injections in either group.

The body weight variation during the 6 months was different between the two groups.

Table II. Metabolic pattern at baseline and 6 month after combined therapy in Group A.

|  | Baseline | 6 months | p (vs baseline) |
|---|---|---|---|
| Body weight (kg) | 67.9 ± 12.91 | 69.81 ± 12.51 | 0.000 |
| FPG (mmol/l) | 14.64 ± 3.76 | 8.72 ± 2.92 | 0.000 |
| HbA$_{1c}$ (%) | 9.10 ± 0.30 | 7.20 ± 0.53 | 0.000 |
| Cholesterol (mmol/l) | 5.45 ± 0.90 | 5.35 ± 1.17 | n.s. |
| Tryglicerides (mmol/l) | 2.20 ± 1.32 | 1.83 ± 1.04 | n.s. |
| Serum uric acid (μmol/l) | 240.89 ± 83.27 | 240.29 ± 72.56 | n.s. |
| Insulin doses (U/kg/day) |  |  |  |
|     Total |  | 0.21 ± 0.13 |  |
|     Rapid |  | 0.062 ± 0.12 |  |
|     Intermediate |  | 0.168 ± 0.12 |  |
| N° injections > 1 (%) |  | 47.42 |  |

Data are means ± SD.

Table III. Metabolic pattern at baseline and 6 month after combined therapy in Group B.

| | Baseline | 6 months | p (vs baseline) |
|---|---|---|---|
| Body weight (kg) | 74.83 ± 11.24 | 73.75 ± 11.33 | n.s. |
| FPG (mmol/l) | 12.05 ± 3.49 | 8.24 ± 3.01 | 0.000 |
| HbA$_{1C}$ (%) | 8.30 ± 0.10 | 6.80 ± 0.13 | 0.000 |
| Cholesterol (mmol/l) | 5.93 ± 1.78 | 5.70 ± 1.53 | n.s. |
| Tryglicerides (mmol/l) | 2.24 ± 1.33 | 1.81 ± 1.09 | n.s. |
| Serum uric acid (μmol/l) | 287.88 ± 70.78 | 301.56 ± 81.48 | n.s. |
| Insulin doses (U/kg/day) | | | |
|    Total | 0.53 ± 0.25 | 0.34 ± 0.2 | 0.000 |
|    Rapid | 0.34 ± 0.22 | 0.21 ± 0.16 | 0.003 |
|    Intermediate | 0.18 ± 0.13 | 0.13 ± 0.09 | 0.000 |
| N° injections > 1 (%) | 91.66 | 83.33 | n.s. |

Data are means ± SD.

In the group A body weight increased significantly (+ 1.94 ± 2.80 kg, p< 0.001 vs baseline), while in group B no gain of body weigth was observed (– 1.07 ± 3.37 kg, p n.s.).

Both groups showed a similar improvement of glycemic control, evaluated considering FPG and HbA$_{1c}$ values.

Plasma cholesterol, triglycerides and uric acid concentrations did not show any significant change in either group.

Total insulin requirement was significantly lower in group A than in group B (0.21 ± 0.13 vs 0.34 ± 0.20 U/Kg/day, p< 0.003) after combined therapy.

Despite of improvement of glycemia, total insulin requirement decreased in Group B from 0.53 ± 0.25 to 0.34 ± 0.2 U/Kg/day after OHAs therapy (p< 0.001).

Short acting insulin requirement was prevalent in the group B, while in the group A intermediate insulin was more frequently requested (Figure 1); thus, in the latter, the bedtime insulin administration alone was preferred, while the most patients of group B needed a second or a third daily insulin injection. No severe hypoglycemic attack was recorded in either group during the 6 months study period.

## Discussion

It is now generally accepted that type 2 diabetes is characterized by both insulin resistance and insulin deficiency[7-9].

In type 2 diabetic subjects in which diet alone doesn't achieve an adequate metabolic control, OHAs improve it by enhancing pancreatic insulin secretion and also by decreasing peripheral insulin resistance[1]. Secondary failure to oral antihyperglycemic agents after an initial favorable response develops as a conseguence of progressive loss of beta-cell function or deterioration of insulin resistance caused by persistent hyperglycemia and possible development of drug resistance. This leads to a need for exogenous insulin therapy[10-12].

On the other hand, there are some conditions of acute glycemic disorders (surgery, cardiovascular event, infectious intercurrent illness, etc.) extablishing the clinical indication for insulin therapy alone in type 2 diabetes[13,14].

Combined therapy (OHAs + insulin) may be a logical treatment regimen in both cases: at the intermediate stage when some response to OHAs is still present in a gradual process of secondary failure of OHAs therapy, and when intercurrent diseases that cause acute glycemic disorders have been resolved.

Our groups were, at baseline, omogeneous for age and duration of diabetes, as well as for their poor glycemic control (expressed by FPG and HbA$_{1c}$ values), lipid and uric acid pattern. The group A patients were tendentially overweight (expression of an uncomplete beta-cell failure); overall, the BMI was higher in the group B (expression of a peripheral hyperinsulinization).

The body weight behaviour, after the six months of observation, was different: the addition of insulin in the group A determined a significant weight restoration, while no weight gain was observed in the group B. In fact, weight gain is very commonly seen in
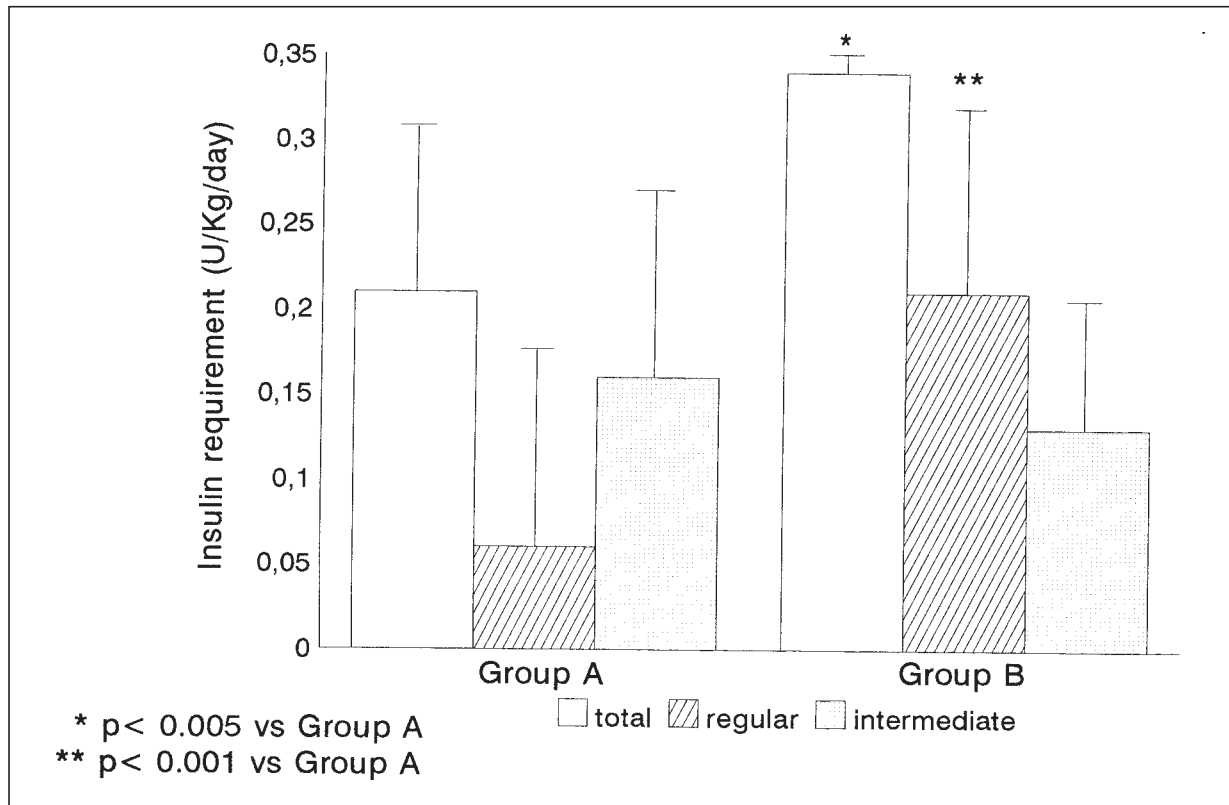
**Figure 1.** Distribution of insulin requirement in the two groups of subjects after combined therapy.

patients after initiation of insulin therapy and has been attributed to decreased calorie loss in the urine, increased appetite, and reduced basal metabolic rate[5]. Indeed, the parameter of body weight and expecially its recent evolution, is a basic element for the possible institution of a combined therapy.

Our results indicate that in both conditions combined therapy is equally effective in improving glycemic control and in maintaining a normal lipid and uric acid pattern, at least during the 6 months period.

It is still not fully defined to what extent, if any, reduction of hyperglycemia will reduce long-term macrovascular complications in NIDDM patients[15,16], while it is well known the key-role of glycotoxicity in determining the beta-cell secretion worsening and the insulin sensitivity impairment[10].

In our study, the total, insulin requirement was lower in the group A; moreover, intermediate insulin dose was lesser in group B than in group A, that received more frequently bedtime insulin, to suppress the excessive nocturnal hepatic glucose production[17,18].

In the group B the total mean insulin requirement was much lower after combined therapy, with prevalence of short acting insulin.

The potential advantage of this approach is improved glycemia with lower doses and multiple administrations of insulin, with a reduced tendency to weight gain and of the risk of hypoglycemic events[5].

Furthermore, a possible disadvantage of insulin therapy alone may be also the theoretical (and highly debated) possibility of accelerated atherosclerosis with peripheral insulin delivery. Co-administration of sulfonylureas improves glycemic control with less peripheral hyperinsulinization, and reduces cardiovascular risk factors including dyslipidemia, hypercolesterolemia, and hypertension[19,20].

In conclusion, in type 2 diabetic patients, therapy with combination of OHAs and insulin was associated with lower insulin doses and less weight gain. Combination treatment may be considered when a partial OHAs failure occurs, and after that insulin therapy alone resolved acute metabolic derangements due to intercurrent diseases.

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