Acta Diabetol (2007) 44:187–192
DOI 10.1007/s00592-007-0004-9

ORIGINAL ARTICLE

Comparison of insulin monotherapy and combination therapy with insulin and metformin or insulin and rosiglitazone or insulin and acarbose in type 2 diabetes

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Received: 23 October 2006 / Accepted: 5 July 2007 / Published online: 29 August 2007

Abstract The aim of this study was to compare the efficacy of treatment with insulin alone, insulin plus acarbose, insulin plus metformin, or insulin plus rosiglitazone in type 2 diabetic subjects who were previously on insulin monotherapy, and to evaluate the effects of these treatments on cardiovascular risk factors including lipid profile, C-reactive protein (CRP) and fibrinogen. Sixty-six poorly controlled type 2 diabetic patients on insulin monotherapy were involved. They were randomized to insulin alone, insulin plus acarbose, insulin plus metformin, or insulin plus rosiglitazone groups for 6 months period. Mean fasting and postprandial glucose values as well as HbA1c levels significantly decreased in all groups. The greatest improvement in HbA1c was observed in insulin plus rosiglitazone (2.4%) and in insulin plus metformin (2%) groups. Daily total insulin dose was increased to 12.7 units/day in insulin alone group, decreased to 4.7 units/day in insulin plus rosiglitazone group, to 4.2 units/day in insulin plus metformin group, and to 2.7 units/day in insulin plus acarbose group. Least weight gain occurred in insulin plus metformin group (1.4 kg) and greatest weight gain occurred in insulin plus rosiglitazone group (4.6 kg). No significant change in lipid levels—except serum triglycerides—was observed in any groups. CRP and fibrinogen levels decreased in all groups, but the decrease in fibrinogen level was significantly greater in insulin plus rosiglitazone group. All groups were comparable in hypoglycemic episodes. No serious adverse event was noted in any group.

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Keywords Type 2 diabetes mellitus · Combination · Insulin · Acarbose · Metformin · Rosiglitazone

Introduction

It is well shown in United Kingdom prospective diabetes study (UKPDS) that tight glycemic control in type 2 diabetics decreases the risk of diabetes-related complications [1]. Besides hyperglycemia, well-recognized traditional risk factors for cardiovascular disease including hypertension, elevated plasma low-density lipoprotein cholesterol (LDL-C) and triglycerides, and high-density lipoprotein cholesterol (HDL-C) levels contribute to increased cardiovascular mortality [1–4]. Newly recognized cardiovascular risk factors including C-reactive protein (CRP), or fibrinogen further increases the cardiovascular risk. Thus the treatment of diabetes requires multi-aimed treatment approach that not only control hyperglycemia effectively but also improves cardiovascular risk factors [5].

Many patients with type 2 diabetes mellitus cannot achieve glycemic control with oral agents and need to be treated with insulin. Studies have shown that insulin therapy, as monotherapy, or in combination with oral antidiabetics, is associated with improved metabolic profile [5]. However, relatively large doses of insulin might be required in insulin resistant patients and associated with substantial body weight gain and an increased risk of hypoglycemia [6]. Three oral insulin-sensitizing drugs, namely metformin, rosiglitazone, and acarbose, are frequently and effectively used to lower blood glucose levels and overcome insulin resistance in type 2 diabetic patients [5]. Metformin is associated with reduced insulin requirements and less weight gain than insulin therapy alone. It

has also several favorable effects on atherotrombotic disease-associated risk factors including LDL-C, plasminogen activator inhibitor-1, and methylglyoxal, which is a precursor of advanced glycation end products. Finally, metformin may also decrease blood pressure [7]. Thiazolidinedione drug rosiglitazone also improves cardiovascular risk profile. The drug has significant improvements on lipid metabolism, fibrinolysis, arterial blood pressure, vascular tone, endothelial function, vascular inflammation, vascular smooth muscle cell proliferation, and intimal media thickness of carotid arteries [7–12]. Although less well studied than metformin, or rosiglitazone, acarbose also improves insulin sensitivity [13, 14].

The use of acarbose, metformin, or rosiglitazone in combination with insulin has demonstrated improved blood glucose control over insulin therapy alone [15–18]. However, direct comparison of insulin alone therapy with acarbose, or metformin, or rosiglitazone in combination with insulin has not been previously designed.

The aim of this study was to investigate the glucose lowering effects of insulin alone, insulin plus metformin, insulin plus rosiglitazone, or insulin plus acarbose in subjects with type 2 diabetes mellitus and determine the type of treatment that would influence the serum levels of total cholesterol, LDL-C, HDL-C, CRP, and fibrinogen in these patients.

Research design and methods

This prospective observational study was conducted at endocrinology outpatient clinic of Baskent University Faculty of Medicine. The institutional ethic committee for human studies approved our study. All participants provided informed consent.

Patients

Subjects with poorly controlled diabetes defined as HbA1C between 7.0 and 14.5% while receiving insulin monotherapy were recruited in the study. Sixty-six consecutive patients aged between 34 and 80 years were included.

Patients who had severe hypertension (higher arterial blood pressure than 180/110 mmHg despite antihypertensive treatment), repeated hypoglycemic episodes, severe cardiovascular and cerebrovascular disease, serum creatine levels higher than 1.4 for women and 1.5 for men, higher hepatic function tests 2.5 times the normal level, abnormal thyroid function tests were excluded from the study. None of the study-included patients had clinical evidence of acute diabetic complications. Incipient heart failure was ruled out by echocardiography examinations. Women who were pregnant or breastfeeding were also excluded from the study. Treatments that could affect glucose metabolism (oral contraceptives, thiazide and loop diuretics, lithium, phenytoin, glucocorticoids, psychotropic drugs, etc.) were not given to patients during the study.

All patients underwent an initial screening assessment that included collection of medical history and a physical examination including waist and hip measurements. Blood samples were obtained from all subjects at baseline and at the end of the 6th month. The parameters measured in fasting serum sample were glucose, HbA1C, total cholesterol, LDL-C, HDL-C, triglyceride, CRP, and fibrinogen. Subjects also provided blood samples for post-prandial glucose measurements.

After the initial assessment, subjects were randomly assigned to continue insulin therapy alone or to add acarbose (300 mg/day), or metformin (1,700 mg/day), or rosiglitazone (8 mg/day) to insulin therapy. All patients received mixed insulin containing 30% insulin aspart plus 70% NPH insulin (NovoMix®30 penfill, or NovoMix®30 flexpen, Novo Nordisk Pharmaceuticals) twice a day. The primary end point was change in HbA1C. Secondary end points were changes in insulin dosage, body weight, waist-to-hip ratio, and lipids. Incidence of hypoglycemia and side effects of treatments were also analyzed.

Follow-up visits were scheduled at 4-week intervals, or more often if necessary to monitor glucose metabolism including fasting and post-prandial glucose values. The optimal dosage of insulin was based on fasting and post-prandial glucose levels at regular follow-up visits. All patients received dietary and lifestyle advice at every follow-up visit by our diabetic care providers.

Patients were instructed to maintain their insulin dose between the follow-up intervals unless hypoglycemia occurred, at which they were instructed to reduce their dose. Patients were also instructed to check blood glucose if they feel hypoglycemic. The number of hypoglycemic events, either symptomatic or based on self-monitoring of blood glucose (defined as <70 mg/dl), was recorded. Severe hypoglycemia was defined as any low plasma glucose level that the patients were unable to treat themselves.

Anthropometric measurements

Measurements of subjects' height, weight, waist, and hip were recorded by the same doctor. Waist circumference was measured with a folding tape at the natural waistline (the level of the umbilicus) in a horizontal plane. Hip circumference was measured as the diameter at the level of the greater trochanters in a horizontal plane. Waist-to-hip

ratio (WHR) was calculated. BMI was obtained by dividing the body weight (kg) to the square of height (m).

Serum analysis

Venous blood samples were drawn after a minimum fasting period of 12 h between 8:00 and 9:00 a.m. Serum glucose was measured by the glucose oxidase technique (Roche Diagnostics GmbH, Mannheim, Germany). Total cholesterol, HDL-C, and triglyceride concentrations were measured by enzymatic assay (Boehringer-Mannheim, Mannheim, Germany). LDL-cholesterol was calculated with the Friedewald formula (LDL-cholesterol = total cholesterol – (HDL-C + triglyceride/5). CRP levels were determined using a latex-enhanced immunonephelometric system in compliance with the manufacturer's instructions (Dade Behring, Marburg, Germany). Fibrinogen was measured using a modified Clauss technique.

Statistical analysis

All continuous data were expressed as mean ± SD. Data were analyzed using the statistical package for the social sciences (SPSS for Windows version 11.0; SPSS Inc., Chicago, IL, USA). Continuous, normally distributed variables were compared with the Student *t* test. One-way ANOVA testing was used for normally distributed values in the comparison with mean values of the four groups. A two-way ANOVA with repeated measurements was used to analyze the effects of treatment time on the studied parameters and to determine whether longitudinal changes in the within-group parameters were significantly different between the four study groups. P values < 0.05 were considered statistically significant.

Results

As noted, the study included total of 66 patients (19 in the insulin alone group, 15 in the insulin plus acarbose group, 17 in the insulin plus metformin group, and 15 in the insulin plus rosiglitazone group). At baseline, age, sex, diabetes duration, daily insulin dose, and HbA1C of all patients were similar among the four groups (Table 1). Anthropometric evaluations also showed no significant differences in height, weight, BMI, waist and hip circumference, and WHR among the groups (Table 1).

Changes in glycemic control, daily insulin requirements, lipid profile, serum levels of CRP, and fibrinogen are given in Table 2.

Changes in glycemic control and daily insulin requirements

There were significant improvements in glycemic control with reduction in HbA1C of 1.2% in insulin alone group, 2% in insulin plus metformin, 2.4% in insulin plus rosiglitazone group and 0.6% insulin plus acarbose group. There was significant difference among groups ($P = 0.002$). The improvement in HbA1C in insulin plus rosiglitazone group was greater than the improvement observed in insulin plus metformin group ($P = 0.002$), insulin plus acarbose group ($P = 0.002$), and insulin alone group ($P = 0.002$). Mean fasting blood glucose ($P = 0.000$) and post-prandial blood glucose levels ($P = 0.000$) decreased in all study groups significantly, but the decrease was comparable between all groups.

Mean total daily insulin dose was significantly increased in insulin alone group compared to baseline (12.8 units/day, $P = 0.000$). Mean total daily insulin dose was significantly decreased at the end of 6 month in insulin plus acarbose group (2.7 units/day, $P = 0.035$), in insulin plus metformin group (4.2 units/day, $P = 0.000$), in insulin plus rosiglitazone group (4.7 units/day, $P = 0.006$).

Body weight gain

Subjects in insulin alone group gained 3.6 ± 3.0 kg, in insulin plus rosiglitazone group 4.6 ± 4.6 kg, in insulin plus acarbose group 2.9 ± 2.7 kg, and in insulin plus metformin group 1.4 ± 3.6 kg. The change in weight was not statistically different between the groups at the end of

Table 1 Characteristics of study patients

	Insulin monotherapy	Insulin plus acarbose	Insulin plus metformin	Insulin plus rosiglitazone
Number of patients	19	15	17	15
Age (year)	61.5 ± 12.0	62.6 ± 6.6	57.7 ± 8.5	57.6 ± 8.8
Duration of DM (year)	17.9 ± 11.5	13.9 ± 7.2	12.1 ± 7.7	12.1 ± 7.9
Sex (F/M)	12/7	8/7	11/6	7/8
BMI (kg/m^2)	28.2 ± 5.9	31.3 ± 3.7	33.2 ± 6.1	30.7 ± 5.6
Waist-to-hip ratio	0.9 ± 0.08	1 ± 0.09	0.9 ± 0.07	0.9 ± 0.09

DM diabetes mellitus, *BMI* body mass index

Table 2 Anthropometric measures, glucose and lipid metabolism, CRP, and fibrinogen levels throughout the study

Parameters	Study period	Insulin monotherapy	Insulin plus acarbose	Insulin plus metformin	Insulin plus rosiglitazone
Weight (kg)	Before	71.7 ± 16.0	81.3 ± 12.2	79.4 ± 14.1	79.7 ± 9.9
	After	75.4 ± 15.1	84.0 ± 12.5	80.8 ± 12.1	84.3 ± 9.4
Waist-to-hip ratio	Before	0.9 ± 0.08	1 ± 0.09	0.9 ± 0.07	0.9 ± 0.09
	After	0.9 ± 0.08	1 ± 0.09	0.9 ± 0.07	0.9 ± 0.06
FBG (mg/dL)	Before	148.8 ± 24.6	138.9 ± 57.2	131.8 ± 17.9	131.4 ± 29.5
	After	107.9 ± 7.4	112.1 ± 10.3	110.8 ± 9.2	113.6 ± 10.4
PBG (mg/dL)	Before	226.0 ± 102.6	201.2 ± 88.5	202.6 ± 77.6	224.4 ± 103.1
	After	184.9 ± 51.7	178.7 ± 74.4	146.0 ± 34.3	159.8 ± 32.0
HbA1c (%)	Before	8.7 ± 1.6	8.3 ± 2.0	8.9 ± 1.2	9.6 ± 1.0
	After	7.6 ± 1.2	7.7 ± 1.8	6.9 ± 1.2	7.1 ± 1.2
Daily insulin dose (IU)	Before	42.7 ± 14.3	54.1 ± 16.3	52.2 ± 13.6	41.9 ± 12.5
	After	55.5 ± 12.0	51.4 ± 16.6	48.0 ± 13.1	37.2 ± 12.2
Total cholesterol (mg/dL)	Before	210.2 ± 70.8	196.6 ± 56.4	177.5 ± 26.5	198.6 ± 34.2
	After	197.1 ± 46.0	194.3 ± 42.4	175.2 ± 25.9	186.1 ± 26.3
Triglyceride (mg/dL)	Before	224.3 ± 211.0	187.2 ± 124.2	151.4 ± 82.0	163.5 ± 96.6
	After	158.8 ± 66.9	159.8 ± 84.0	134.9 ± 58.0	133.8 ± 68.4
LDL-C (mg/dL)	Before	123.9 ± 32.3	115.5 ± 39.1	99.3 ± 22.0	122.1 ± 20.4
	After	115.7 ± 24.7	122.4 ± 29.0	101.5 ± 21.4	110.2 ± 24.4
HDL-C (mg/dL)	Before	49.2 ± 7.8	47.0 ± 10.9	52.3 ± 15.7	46.0 ± 12.3
	After	49.4 ± 6.6	48.7 ± 9.7	52.2 ± 14.5	49.3 ± 7.5
CRP	Before	4.8 ± 3.4	6.1 ± 6.8	3.7 ± 3.6	5.4 ± 3.8
	After	4.3 ± 2.8	4.8 ± 4.3	2.5 ± 2.7	2.7 ± 1.5
Fibrinogen	Before	323.2 ± 59.2	312.2 ± 61.2	324.0 ± 62.8	342.6 ± 58.0
	After	302.9 ± 54.6	298.0 ± 52.2	304.5 ± 63.6	295.9 ± 51.0

FBG fasting blood glucose, *PBG* post-prandial blood glucose, *LDL-C* low density lipoprotein cholesterol, *HDL-C* high density lipoprotein cholesterol, *CRP* C-reactive protein

study. BMI was also increased significantly in all groups ($P = 0.000$), but the change in BMI was not significantly different between four groups. WHR did not change significantly in all groups.

Lipid levels

No significant difference in total cholesterol, LDL-C, and HDL-C, levels were observed in all study groups. But serum triglyceride levels decreased significantly ($P = 0.009$) which was comparable between the groups.

C-reactive protein and fibrinogen levels

At 6 months, CRP levels decreased significantly in all groups ($P = 0.01$) but did not differ significantly between the groups. Fibrinogen levels also decreased significantly in all groups ($P = 0.000$), but the decrease was greater in insulin plus rosiglitazone group than insulin plus metformin group ($P = 0.033$), insulin plus acarbose group ($P = 0.033$), and insulin alone group ($P = 0.033$).

Adverse events

None of the subjects discontinued treatment. Only three patients in insulin plus metformin group experienced gastrointestinal side effects, which were resolved within few weeks. Two patients of insulin plus acarbose group had flatulence and bloating. There were no significant differences among the groups in the rate of hypoglycemic episodes. Hypoglycemic episodes were observed in one patient in insulin plus acarbose group. Two patients in each remaining group experienced hypoglycemic episodes. None of the patients experienced severe hypoglycemia. Pretibial edema was seen in one patient both in insulin alone group and insulin plus rosiglitazone group.

Discussion

Our study demonstrated that insulin as monotherapy, or in combination with metformin, or rosiglitazone, or acarbose therapy improved glycemic control and resulted in a decrease in HbA1C levels. Subjects treated with insulin plus rosiglitazone and insulin plus metformin groups had similar HbA1C reductions. Only in insulin monotherapy group, patients required significantly more insulin from baseline to achieve improved glycemic control. However, subjects in the groups receiving insulin alone and insulin combined with acarbose, or rosiglitazone gained, not significant, more weight than insulin plus metformin group.

Combination of insulin and acarbose improved glycemic control in our study. Only 0.6% reduction in HbA1C level was observed in this group and 5% less insulin was required at the end of the study. Body weight gain was 2.8 kg. There was also improvement in serum triglyceride, CRP, and fibrinogen levels. However, in previous studies combination therapy with insulin and acarbose resulted in much improvement in glycemic control in type 2 diabetic patients [6, 14, 15, 19]. While some studies demonstrated significant reduction in total daily insulin dose, some others did not. Guvener et al [14] also demonstrated significant reduction in LDL-cholesterol levels in their study. But there are contrasting results regarding the effect of insulin plus acarbose therapy on lipid levels in the literature [13, 14, 19, 20]. Our findings of significant decrease in CRP and fibrinogen levels in insulin plus acarbose group were similar with previous studies [13].

Insulin plus metformin combination caused a 2% reduction in HbA1C level and 8% reduction in total daily insulin dose. Weight gain was 1.4 kg. These findings were consistent with the previous studies [18, 21]. In most of the studies reduced insulin requirements and less weight gain were noted as in our study. Some studies also reported improvement in lipid profile as well as other cardiovascular risk factors including CRP and fibrinogen in patients receiving metformin alone, or in combination with other therapies [7, 18, 21, 22]. In our study there was a significant improvement in serum triglyceride level, which was not different between the groups. Also a significant improvement was observed in CRP and fibrinogen levels.

In our study, the reduction in HbA1C level was greatest in insulin plus rosiglitazone group, which was 2.4%. Reduction in total daily insulin dose was 11%, significantly greater than the other three groups. A weight gain of 4.6 kg was noted throughout the study period. There was improvement in serum triglyceride levels also. Our findings accord with previous studies regarding the effect of rosiglitazone on glycemic control and weight gain [11, 23–25]. Most of these studies also reported that treatment with rosiglitazone improved lipid profile and cardiovascular risk factors including CRP and fibrinogen, and reduced total daily insulin requirements [9, 11]. In comparison of troglitazone and metformin for cardiovascular risk factors, troglitazone treatment was found to increase size of small dense LDL-C causing less atherogenic particle structure. Also decreases in fibrinogen, PAI-1, and CRP levels occurred [7, 18, 22]. In our study the impressive decrease in fibrinogen levels in insulin plus rosiglitazone group was significantly greater than the decrease occurred in insulin plus metformin group.

In general hypoglycemia was infrequent, mild, and self limited in all four groups in our study. All four-treatment regimens were well tolerated and frequency of adverse events was acceptable.

In conclusion, the combination of insulin with rosiglitazone, or metformin is a good alternative for poorly controlled type 2 diabetic patients who are on insulin monotherapy. Both treatment combination enhanced glycemic control, decreased required total daily insulin dose, and had significant improvement in CRP and fibrinogen levels. These combinations also had beneficial effects on serum triglyceride levels. However, long-term studies with larger population will be needed to determine whether improvements in these cardiovascular risk factors will translate into reduced cardiovascular disease.

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