The Combined Effect of Triple Therapy With Rosiglitazone, Metformin, and Insulin Aspart in Type 2 Diabetic Patients

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OBJECTIVE — Type 2 diabetes is caused by reduced insulin secretion and insulin resistance in skeletal muscle and liver. We tested the combination therapy with insulin aspart, rosiglitazone, and metformin with the purpose of treating all three defects in order to test the hypothesis that this “triple therapy” will normalize glucose metabolism.

RESEARCH DESIGN AND METHODS — Sixteen obese type 2 diabetic outpatients on human NPH or MIX (regular + NPH insulin) insulin twice daily were randomized to either triple therapy, i.e., insulin aspart (a rapid-acting insulin analog) at meals, metformin (which improves hepatic insulin sensitivity), and rosiglitazone (which improves peripheral insulin sensitivity), or to continue their NPH or MIX insulin twice daily for 6 months. Insulin doses were adjusted in both groups based on algorithms. HbA1c, insulin dose, hypoglycemic episodes, insulin sensitivity (clamp), hepatic glucose production (tracer), and diurnal profiles of plasma glucose and insulin were used in evaluating treatment.

RESULTS — In the triple therapy group, HbA1c declined from 8.8 to 6.8% (P < 0.01) without inducing severe hypoglycemic episodes. Postprandial hyperglycemia was generally avoided, and the diurnal profile of serum insulin showed fast and high peaks without any need to increase insulin dose. In the control group, the insulin dose was increased by 50%, but nevertheless both HbA1c and 24-h blood glucose profiles remained unchanged. Insulin sensitivity improved in both skeletal muscle and the liver in the triple therapy group, whereas no change was observed in the control group.

CONCLUSIONS — We conclude that treatment of the three major pathophysiological defects in type 2 diabetic subjects by triple therapy significantly improved glucose metabolism in obese type 2 diabetic subjects.

Diabetes Care 26:3273–3279, 2003

Type 2 diabetes is a common fast-growing disease that affects about 5% of the population worldwide. The disease is complicated by specific cardiovascular events, and the mortality rate is 2–3 times higher than in the background population (1).

The U.K. Prospective Diabetes Study (UKPDS) clearly showed that intensive care matters because the intensive treatment group developed fewer diabetes-related end points (2). Despite that, most type 2 diabetic subjects are still in poor control and far from recommended HbA1c values, i.e., <6.5–7.0% (3,4). Thus, in a multinational European study, mean HbA1c values for 10 different countries were found to be ~8.1% (5). However, in several published intervention studies, the value in insulin-treated subjects is even higher, i.e., ~9–10% (6).

Pharmacological treatment is needed in >80% of type 2 diabetic subjects. In this context, there has been a tradition for many years to use only one anti-diabetic drug at a time, and most patients are still treated with either insulin secretagogues or insulin alone. However, these drugs have only a minor effect on cardiovascular events and mortality (2), whereas metformin, which improves insulin sensitivity, is able to reduce the risk of myocardial infarction and reduce the mortality rate (7,8). Altogether, the UKPDS showed that for each percentage-point reduction in HbA1c, diabetes complications and the mortality rate declined by 21% (9). Therefore, normalization of HbA1c must be a major goal in the treatment of type 2 diabetic subjects.

Three pathophysiological components seem to be of major importance in the development of hyperglycemia in obese adults. These are peripheral insulin resistance (i.e., reduced insulin-mediated glucose uptake in skeletal muscle), insulin resistance in the liver (resulting in inappropriate glucose production), and an impaired insulin response to glucose resulting in reduced and delayed insulin peaks in relation to mixed meals (3,10,11). The purposes of this study were to 1) evaluate whether improvement of insulin sensitivity in skeletal muscle and liver, together with restoration of the normal insulin response to a meal as applied by triple therapy (rosiglitazone, metformin, and insulin aspart), may improve glucose metabolism in type 2 diabetic subjects (12–14) and 2) test if this therapy was better than standard therapy with NPH insulin with regard to glucose and fat metabolism.
NPH or MIX insulin twice daily were recruited from our university diabetes clinic for this investigator-initiated study (Table 1). The study was approved by the local ethical committee and by the Danish Medicines Agency. All subjects gave written informed consent. The inclusion criteria were age 40–76 years, fasting serum C-peptide >250 pmol/l, BMI 25–40 kg/m², HbA₁c >7%, and insulin therapy, whereas the exclusion criteria were s-creatinine >100 μmol/l, plasma alaninaminotransferase >100 units/l, intolerance to metformin, left ventricular ejection fraction measured with echocardiography <40%, blood pressure >180/100 mmHg, severe dyslipidemia (total cholesterol >8 and triglyceride >5 mmol/l), and unawareness of hypoglycemia. A reference material of age- and BMI-matched nondiabetic control subjects (11) was used in comparison with the degree of insulin resistance (Table 1).

Design
At inclusion, subjects were matched for HbA₁c, and age and were thereafter block randomized into two groups of eight subjects, the triple therapy group or to continued NPH or MIX insulin therapy (control group) (Table 1). During a 2-month start-up period, when the pre-tests were carried out, the treatment was unchanged in both groups. A total of seven patients already received metformin before randomization, three in the control group and four in the triple therapy group.

Following randomization, the control group continued their insulin regimen (and the three control group patients using metformin before randomization also continued this treatment), but the insulin dose was increased to obtain the best possible metabolic control. The aims for the control group were blood glucose within the range of 5–7 mmol/l preprandial and HbA₁c <7% without inducing severe hypoglycemia (i.e., events needing help from another third person). One to two mild hypoglycemic events were accepted per week. Self-monitored blood glucose (SMBG) was measured four times per day, before meals and at bedtime.

The triple therapy group started with rosiglitazone (Avandia) 4 mg/day (dose was increased to 8 mg/day after 8 weeks), metformin (Glucophage) 0.5 g twice per day (dose was increased after 4 weeks to 1 g twice daily), and insulin aspart (NovoRapid) three times per day injected just before each main meal. Initially, total daily insulin dose was reduced to one-third of the dose given during the start-up period to avoid hypoglycemia during the start of treatment with rosiglitazone and metformin, and it was divided into three equal doses. In the triple therapy group, the target SMBG values were 5–7 mmol/l postprandial (measured 1.5 h after each meal) and HbA₁c <7%, with no severe hypoglycemic events but one to two mild events were accepted per week.

The insulin dose in both groups was adjusted by the diabetologist at scheduled visits and at scheduled telephone contact (five outpatient clinic visits and two telephone contacts) and kept constant in the last 2 months of the study period. Thus it was possible to change insulin dosages seven times during the study. Overall, insulin dose was adjusted as follows: a reduction in total insulin dose of ~10% if mean blood glucose was <5 mmol/l, unchanged if blood glucose was 5–7 mmol/l, and increases in insulin dose of ~5–10% if blood glucose was 7–10 mmol/l, 10–20% if blood glucose was 10–13 mmol/l, and 20–30% if blood glucose was >13 mmol/l. In the control group, the morning insulin dose was changed mainly based on prelunch, predinner, and nighttime SMBG values, whereas the late insulin dose was changed mainly based on fasting SMBG values, whereas the late insulin dose was changed mainly based on fasting SMBG values, whereas the late insulin dose was changed mainly based on fasting SMBG values, whereas the late insulin dose was changed mainly based on fasting SMBG values, whereas the late insulin dose was changed mainly based on fasting SMBG values, whereas the late insulin dose was changed mainly based on fasting SMBG values, whereas the late insulin dose was changed mainly based on fasting SMBG values, whereas the late insulin dose was changed mainly based on fasting SMBG values, whereas the late insulin dose was changed mainly based on fasting SMBG values, whereas the late insulin dose was changed mainly based on fasting SMBG values, whereas the late insulin dose was changed mainly based on fasting SMBG values, whereas the late insulin dose was changed mainly based on fasting SMBG values, whereas the late insulin dose was changed mainly based on fasting SMBG values, whereas the late insulin dose was changed mainly based on fasting SMBG values.

Subjects were asked not to change their diet and exercise level during the study period. HbA₁c was measured every second month, and a 24-h profile of blood glucose, serum insulin, serum C-peptide, and plasma free fatty acid (FFA) was carried out before and after 6 months of treatment. Insulin sensitivity was measured before and after the 6-month treatment period.

Analytical procedures
Euglycemic-hyperinsulinemic clamp study. This test was performed as previously described by Hother-Nielsen et al. (15). A primed-constant intravenous infusion of 3-3H-glucose (DuPont-New England Nuclear, Boston, MA) was started in the morning and continued throughout the entire study. The ratio of priming dose (10 ml) and constant infusion (0.1 ml/min) was 100 (15). To achieve a common level of basal plasma-specific activity, the tracer infusion was adjusted for surface area by adjustment of the infusion volume (16). After a 120-min basal tracer equilibration period, insulin (Actrapid Human; Novo Nordisk) was infused at a rate of 40 mU · min⁻¹ per m² body surface area for 240 min. After initiation of the infusion, the plasma glucose concentration was allowed to fall to 5.5 mmol/l, at which level it was maintained (clamped) using a variable infusion of 20% glucose enriched with 3-3H-glucose to maintain the specific activity constant at baseline levels during the clamp (17).

Continuous indirect calorimetry, using a ventilated hood system (Deltatrac 2; SensorMedics, Yorba Linda, CA) was performed during the last 40 min of the basal and insulin infusion periods. Urine samples for determination of the urea excretion were obtained from the start to the

### Table 1—Baseline clinical and biochemical characteristics of the study groups

<table>
<thead>
<tr>
<th></th>
<th>Control group</th>
<th>Triple therapy group</th>
<th>Reference material</th>
</tr>
</thead>
<tbody>
<tr>
<td>n (male/female)</td>
<td>8 (4/4)</td>
<td>8 (3/5)</td>
<td>10 (8/2)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>61 ± 2</td>
<td>66 ± 4</td>
<td>56 ± 3</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>31.3 ± 1.9</td>
<td>32.1 ± 2.1</td>
<td>29.0 ± 0.5</td>
</tr>
<tr>
<td>HbA₁c (%)</td>
<td>9.1 ± 0.4</td>
<td>8.8 ± 0.9</td>
<td>5.4 ± 0.1</td>
</tr>
<tr>
<td>Fasting blood glucose (mmol/l)</td>
<td>10.3 ± 1.1</td>
<td>9.3 ± 1.3</td>
<td>5.3 ± 0.1</td>
</tr>
<tr>
<td>Fasting serum insulin (pmol/l)</td>
<td>104 ± 10</td>
<td>104 ± 14</td>
<td>30 ± 6</td>
</tr>
<tr>
<td>Fasting serum C-peptide (pmol/l)</td>
<td>585 ± 103</td>
<td>715 ± 152</td>
<td>509 ± 50</td>
</tr>
<tr>
<td>Insulin dose per day (units/kg body wt)</td>
<td>0.46 ± 0.16</td>
<td>0.42 ± 0.16</td>
<td>0</td>
</tr>
<tr>
<td>Duration on diabetes (years)</td>
<td>7.3 ± 0.9</td>
<td>10.9 ± 2.6</td>
<td>0</td>
</tr>
<tr>
<td>Years on insulin</td>
<td>3.3 ± 1.2</td>
<td>5.1 ± 2.0</td>
<td>0</td>
</tr>
</tbody>
</table>

Data are means ± SE.
end of the euglycemic-hyperinsulinemic clamp for calculation of protein oxidation rates. 

Diurnal profiles of glucose, insulin, C-peptide, and FFA. Beginning at 8:00 A.M., one catheter was inserted into an antecubital vein for blood sampling of blood glucose, serum insulin, serum C-peptide, and plasma FFA. Blood samples were obtained right before each main meal (breakfast, lunch, and dinner) and then 30 min, 1, 1.5, 2, 2.5, and 3 h later and thereafter every hour until the next meal. At night, blood samples were obtained at 3:00 and 7:00 A.M.

Assays. Plasma glucose concentration was measured using the glucose oxidation method (Glucose Analyzer 2, Beckman Instruments). HbA1c was measured by a high-performance liquid chromatography method (Tosho Alc 2.2, Tosho Bioscience, Japan) (normal range 4.4–6.4%). Serum insulin and C-peptide samples were analyzed by a two-site, time-resolved immunofluorometric assay (DELFIA) (18). Insulin aspart was measured with a modification of the method described by Andersen et al. (19). Plasma FFA concentrations were measured by Itaya et al.’s method (20). Plasma total cholesterol, HDL cholesterol, and triglyceride concentrations were measured by a kit from Boehringer Mannheim (Diagnostica, Mannheim, Germany), and LDL cholesterol was calculated using the Friedewald equation. Tritiated glucose-specific activity was determined on barium/zinc deproteinized plasma samples as previously described.

Calculations
Rates of glucose appearance ($R_A$) and rates of glucose disappearance ($R_D$) were calculated using Steele’s non–steady-state equations, using a distribution volume of 200 ml/kg (21) and a pool fraction of 0.65 (22). Glucose storage rate was calculated as $R_D$ minus the glucose oxidation rate. The insulin sensitivity index ($S_I$) was calculated as $R_D$ divided by incremental increase in serum insulin concentration during the insulin clamp and divided by the mean glucose concentration during the last hour of the insulin clamp. Hepatic glucose production (HGP) was calculated as: $HGP = R_A - \text{glucose infusion rate}$.

Statistical analysis
Results are presented as means ± SE unless otherwise stated. Differences between the groups or within a group were compared by unpaired or paired T tests. Correlation analysis was performed using Pearson correlation analysis. Statistical analysis was performed using SPSS for Windows (version 10.0). $P$ values <0.05 were considered significant.

RESULTS
Glucose metabolism (HbA1c and diurnal profile of blood glucose)
HbA1c did not change in the control group during the study period, whereas in the triple therapy group, a marked reduction was observed (8.8 ± 0.9 to 6.8 ± 0.3%, $P = 0.004$) (Fig. 1). Thus, at the end of the study period, HbA1c levels in the triple therapy group were close to the reference value (4.4–6.4%) and were 2.0% points better than in the control group on twice daily insulin treatment ($P < 0.001$). Twenty-four-hour blood glucose profiles were sampled before and after 6 months of intervention (Fig. 2A). Before intervention, the two curves were superimposable (data not shown), but after intervention, blood glucose in the triple therapy group was <6 mmol/l during most of the 24-h period, and the postprandial peaks of hyperglycemia were generally eliminated. During the night, glucose values increased slightly in both groups and to a slightly higher level in the triple therapy group. However, the fasting blood glucose concentrations in the morning in the two groups after 6 months of intervention were identical (7.8 ± 0.9 and 8.2 ± 0.8 mmol/l, respectively).

Insulin dose and serum insulin values
In the control group, the insulin dose was increased gradually and reached the level of 0.67 ± 0.24 units · kg body wt$^{-1}$ · day$^{-1}$ (at inclusion 0.46 ± 0.16 units · kg body wt$^{-1}$ · day$^{-1}$, $P < 0.03$), whereas the insulin dose following intervention was unchanged in the triple therapy group (0.29 ± 0.11 vs. 0.42 ± 0.16 units · kg body wt$^{-1}$ · day$^{-1}$) despite improvement in metabolic control and being significantly lower than the insulin dose in the control group ($P < 0.002$). The diurnal profiles of serum insulin were superimposable in the two groups before intervention (data not shown). After 6 months, the pattern for the control group was unchanged, but the diurnal level was increased (Fig. 2B). However, after 6 months, the triple therapy group showed clearly defined insulin peaks at meal times. The peaks rose rapidly up to 400 pmol/l after 60 min and thereafter rapidly reduced again in the pattern quite similar to that seen in nondiabetic subjects (Fig. 2B). The insulin peaks were mainly due to the insulin aspart injections (Fig. 2C). These measurements also showed that insulin aspart given with the evening meal was cleared again before midnight. Therefore, plasma insulin concentrations during the night were much lower in the triple therapy group than in the control group. This difference may be a safeguard against nocturnal hypoglycemia.

Insulin resistance, glucose oxidation, and HGP
After 6 months of intervention, glucose infusion rates in the triple therapy group rose significantly from 101.8 ± 22.0 to
166.5 ± 11.8 mg min⁻¹ m⁻², (P < 0.02); however, insulin sensitivity was still below the level for the nondiabetic reference group (170 ± 20 mg min⁻¹ m⁻²). When insulin sensitivity was estimated by the “tracer technique,” $S_i$ for the triple therapy group was found to increase too, and this increase was mainly due to an increase in glucose oxidation and not in glucose storage (Table 2). In accordance with this, lipid oxidation during the insulin clamp decreased significantly (Table 2). Interestingly, lipid oxidation during the clamp correlated with mean diurnal FFA concentration in the combined group of patients ($R = 0.65, P < 0.01$).

During intervention in both groups, HGP was suppressed to the normal level (nondiabetic control group: 21 ± 3 mg min⁻¹ m⁻²) but at lower serum insulin values in the triple therapy group than in the control group, indicating improved liver insulin sensitivity during treatment in the triple therapy group (Table 2).

**Body weight, blood pressure, lipids, and safety**

Body weight increased nonsignificantly by 1 kg in the control group and 3 kg in the triple therapy group ($P > 0.1$). Blood pressure and lipids did not change significantly (Table 2). Fasting plasma FFA values were identical before and after intervention in the triple therapy group. However, during the 24-h profile mean diurnal plasma FFA values were lower in the triple therapy group compared with the control group ($22.7 ± 1.4$ vs. $33.5 ± 4.7$ mmol/l, $P = 0.057$).

A slight decrease in the hemoglobin concentration in the triple therapy group was found (Table 2), and interestingly, plasma alaninaminotransferase values decreased (but not statistically significantly), which may be caused by a reduction of fat content in the liver.

One subject in the triple therapy group stopped treatment due to subjective sensation of fluid retention but no peripheral edema was demonstrated and X-ray of the chest was without sign of pulmonary edema.

**Hypoglycemia**

Despite the increased insulin dose in the control group and the improvement of metabolic control in the triple therapy group, no severe hypoglycemic attacks were reported in either group. In the last 2 months, when the insulin dose was maintained constant and glucose levels were stable, one mild hypoglycemic event was reported in the control group and a total of seven events (in two subjects only) in the triple therapy group ($P > 0.1$). No nocturnal episodes were registered.

**CONCLUSIONS**

In this study of poorly controlled, long-term type 2 diabetic subjects with severe insulin resistance and abolished first-phase insulin response, we found that a new concept of treatment with insulin aspart, metformin, and rosiglitazone based on pathophysiological knowledge was able to significantly improve the HbA1c level without inducing severe hypoglycemia. In fact, the regimen may be a safeguard against nocturnal hypoglycemia. No changes in
body weight, blood pressure, or lipid profile were observed. The only side effect recognized was a 7% reduction of the hemoglobin concentration. This new concept shows interesting potential, but of course long-term studies are needed to prove this (these studies have already been initiated in Denmark).

**Test of hypothesis**

Our primary aim was to test the hypothesis that normalization of the three major defects in the pathophysiology of type 2 diabetes may result in near normalization of blood glucose. We found that the HbA1c levels in the triple therapy group after 6 months improved significantly. Furthermore, the 24-h glucose values measured at home (SMGB) and during a 24-h profile in the hospital (Fig. 2A) showed a glucose pattern close to that found in normal subjects with geometric mean values of about 7 and 6 mmol/l, respectively. Thus, our study seems to confirm the hypothesis that restoration of the three pathophysiologic defects in type 2 diabetic subjects may improve the blood glucose profile.

Insulin sensitivity was not completely normalized in the triple therapy group compared with a nondiabetic population, but insulin aspart at mealtime was able to mimic a normal insulin profile with rapid and high insulin peaks. This resulted in no postprandial glucose elevation after breakfast and lunch and minor elevation after dinner. These findings demonstrate the importance of a normal insulin profile but also show that improvement of postprandial glucose values has an impact on the 24-h glucose profile as well as on fasting blood glucose. Moreover it shows the putative impact of postprandial hyperglycemia on HbA1c.

With respect to nocturnal hypoglycemia, triple therapy seems to be safe because the risk is very low. The reason for this is insulin aspart, which disappears from the blood during the evening and is therefore only endogenous insulin that is present at night. If blood glucose declines at night, endogenous insulin secretion declines as well.

In the control group, HbA1c values did not improve significantly despite a 50% increase in NPH or MIX insulin dose. The explanation for this is primarily that these subjects have severe insulin resistance; some received 100 units/day of insulin. The reason for the high HbA1c values despite high doses of NPH insulin could be that postprandial hyperglycemia is not avoided by 1–2 injections of NPH insulin per day, as indicated in a recent study by Yki Järvinen et al. (23). Thus, NPH insulin once or twice daily seems unable to normalize blood glucose values. It could be argued that the dose of insulin in the control group was still not high enough to produce a normal glycemic response. However, our study demonstrates that with triple therapy postprandial glucose and HbA1c decreased without an increase in insulin dose, which is completely opposite to what is seen in the control group. Therefore, the answer to our secondary aim is that triple therapy is associated with a lower HbA1c level than treatment with NPH or MIX insulin, at least in the present study setup.

**Clinical experience with combination therapy in type 2 diabetes**

In the literature, we found 25 studies on combination therapy in type 2 diabetes, i.e., a combination of NPH insulin and either metformin, sulphonylureas, acarbose, or glitazone running for time peri-
Triple therapy in type 2 diabetes

ods of 3–12 months. Overall, after treatment in these studies, HbA1c levels only decreased to a value of ~9% (6). Thus, the results of the combination of NPH insulin and one oral antidiabetic drug have not been encouraging. The combination of NPH insulin at night with metformin twice daily seems the most appropriate treatment for the moment, but even in the best of these studies, the HbA1c levels are 1.2% above the upper level for control subjects (6).

Only two studies on the effect of rapid-acting insulin before meals have been carried out in type 2 diabetic subjects. In a controlled study, the combination of regular insulin at meals and a sulphonylurea was not better than NPH insulin alone (24). A similar result was obtained with the combination of insulin lispro at meals with a sulphonylurea in comparison with the combination of NPH insulin with a sulphonylurea (25). Altogether, the literature and our results suggest that triple therapy seems superior to other regimes, yet it has to be tested in larger studies against different combinations of treatment.

Peripheral insulin resistance

Type 2 diabetic subjects are insulin resistant, i.e., insulin-mediated glucose disposal is significantly reduced, as also demonstrated in this study (10). This defect seems to be allocated to skeletal muscle, where glucose uptake, disposal, and oxidation are reduced. In this study, glucose oxidation during treatment in the control group was unchanged, whereas glucose oxidation improved significantly in the triple therapy group (Table 2). This makes sense because an increase in glucose oxidation is mandatory for a decline in blood glucose values. The increase in glucose oxidation may be mainly explained by rosiglitazone treatment (26). In accordance with this, FFA levels during the day were reduced during treatment with triple therapy, and the mean FFA concentration correlated with lipid oxidation during the clamp. This may be mainly explained by the treatment with rosiglitazone.

HGP

Basal HGP has been reported to be slightly increased (by about 15%) in untreated type 2 diabetic subjects (11,27). In this study, fasting HGP was slightly increased compared with nondiabetic reference material. After 6 months, fasting HGP was still within the normal range despite a decline in fasting serum insulin in the triple therapy group, indicating that other variables also play an important role in fasting HGP. The action of HGP during the insulin clamp was estimated at only two insulin concentrations in this study, but the results indicate that the liver is also insulin resistant and that the treatment increases hepatic insulin sensitivity in the triple therapy group. The improvement of insulin sensitivity in the liver may be related mainly to metformin treatment (26).

Body weight, blood pressure, liver function, and safety

Body weight increased slightly but non-significantly. Improved metabolic control can by itself account for an increase in body weight. Yki Jarvinen (6) calculated that a 1% decrease in HbA1c level results in a 2-kg increase in body weight. Thus, there is no reason to anticipate that rosiglitazone should have increased body weight specifically. However, if so, this effect may have been counterbalanced by metformin treatment.

Blood pressure and plasma triglyceride did not change significantly, and there was no difference between the groups. Specifically, there was no increase in LDL cholesterol in either group. Rosiglitazone did not induce any degree of liver toxicity whatsoever. One subject stopped the triple therapy after several months due to a subjective feeling of edema, but objective signs of edema were not found and X-ray of the chest was normal. The only recognized side effect was the well-known reduction in hemoglobin concentration.

Design

The main aim in this study was to test a hypothesis, and this does not involve a controlled blinded protocol. However, a subaim was to study if the chosen concept, i.e., triple therapy, was better than treatment with NPH or MIX insulin twice daily. Such a study should ideally be blinded, but that is impossible if you choose to give both groups the benefit of changing insulin dosages during the study period. Furthermore, in a blinded trial, syringes with saline should have been used, from which ethical considerations arise. By offering both groups identical care, applying identical goals for the metabolic control in both groups, and using insulin algorithms, we feel that we have compensated for the missing blinding, and therefore a bias in favor of the triple therapy group has been minimized. One year after completion of the study, five subjects still receive triple therapy, and these subjects’ glycemic control is nearly identical to what it was at the end of the study (6.7 ± 0.4 vs. 6.6 ± 0.3%), whereas seven subjects in the control group have continued conventional treatment with no improvement in HbA1c over time (8.8 ± 0.4 vs. 9.2 ± 0.8%).

In conclusion, we have shown that 6 months of treatment with a new concept based on our available pathophysiological knowledge (rosiglitazone, metformin, and insulin aspart) significantly reduced the 24-h glucose profile and the HbA1c level. No significant increase in body weight and no impairment in plasma lipids, blood pressure, and safety parameters (hemoglobin was an exception) were observed in the triple therapy group.

These results strongly indicate that normalization of the three major pathophysiological defects of type 2 diabetic subjects, namely peripheral insulin resistance, hepatic insulin resistance, and reduced insulin response following meals can significantly improve glucose metabolism. Triple therapy seems a promising treatment for hyperglycemia in type 2 diabetic subjects, but long-term studies are necessary. However, if these results are confirmed, diabetes complications may be dramatically reduced.

Acknowledgments—Insulin aspart was kindly supplied by Novo Nordisk, Denmark, rosiglitazone by GlaxoSmithKline, U.K., and metformin by Merck, U.K. This study was supported by grants from the Clinical Institute, University of Southern Denmark, Bernard Rasmussen and wife Meta Rasmussen’s foundation, Overlægerødet Legatudvalg, Den Almindelige Danske lægeforening’s science foundation, Novo Nordisk, Denmark, and GlaxoSmithKline, Denmark.

The authors gratefully acknowledge Klaus Levin, Kurt Højlund, Tony Bill Hansen, Jørgen Hangard, Knud Erik Pedersen, Karin Dreygaard, Charlotte Olsen, Lone Hansen, and Eva Lund for their valuable contributions. A special thanks to Ole Blaabjerg for developing the insulin aspart assay.

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