Treatment of Type 2 Diabetes With Combined Therapy

What are the pros and cons?

MASSIMO MASSI-BENEDETTI
MARCO ORSINI-FEDERICI

Type 2 diabetes is a progressive syndrome that evolves toward complete insulin deficiency during the patient's life. A stepwise approach for its treatment should be tailored according to the natural course of the disease, including adding insulin when hypoglycemic oral agent failure occurs. Treatment with insulin alone should eventually be considered in a relevant number of cases. Experience has shown the protective effects of insulin on β-cell survival and function, resulting in more stable metabolic control. On the contrary, treatment with most insulin secretagogues has been associated with increased β-cell apoptosis, reduced responsiveness to high glucose, and impairment of myocardial function during ischemic conditions. In addition, macrovascular complications are associated with postprandial hyperglycemia, indicating the need for tight glycemic control. Insulin treatment, especially with rapid-acting analogs, has been demonstrated to successfully control postprandial glucose excursions. Finally, a reason for concern with regard to combined therapy is represented by the evidence that polipharmacy reduces compliance to the treatment regimen. This can be particularly relevant in patients with type 2 diabetes usually taking drugs for complications and for concomitant diseases with consequent deterioration not only of metabolic control but also of other conditions. In conclusion, therapy with insulin alone immediately after hypoglycemic oral agent failure may be a useful and safe therapeutic approach in type 2 diabetes.

Diabetes Care **31 (Suppl. 2):S131–S135, 2008**

Type 2 diabetes results from the combination of insulin resistance and insulin deficiency, for which balance varies during the natural course of the disease (1–3). Insulin resistance is predominant in pre-diabetes and in the early stages of clinically evident diabetes, whereas insulin deficiency becomes prevalent in later stages of the disease (4). This evolution influences the therapy paradigm that usually follows a stepwise approach (5). The initial step for the treatment of type 2 diabetes consists of a tailored diet and physical exercise regimen that may lead to an improvement of metabolic control and to a reduction of the risk of hypertension and cardiovascular disease (6,7). When lifestyle interventions fail to normalize blood glucose, metformin is typically introduced as first-line therapy (8). Sulfonylureas, which in the past have been widely used as a first choice in oral treatment, are at present considered as a second-line choice for combined therapy when metformin does not maintain metabolic targets (9). Glitazones can be used as second-line therapy in association with metformin or sulfonylureas, although they are more frequently prescribed in the early stages of the disease as first-line monotherapy. In this scenario, the use of insulin is considered when optimized oral therapy is unable to maintain glucose control at target levels. The primary goal of insulin therapy is to reduce A1C levels to prevent or delay the progress of chronic complications. When initiating chronic insulin therapy in type 2 diabetes, the question arises whether it is more profitable to maintain or not to maintain the oral therapy. A number of original studies and meta-analysis show the benefits of the combination of oral agents and insulin in achieving metabolic targets and lowering the possible negative effects and risks such as reduction of insulin sensitivity, hypoglycemia, and weight gain (10–13).

However, type 2 diabetes is a progressive disease, characterized by a progressive decline of β-cell function up to its exhaustion, which leads to the need of insulin as sole therapy. The U.K. Prospective Diabetes Study has shown that during 6 years, >50% of subjects who were randomized to sulfonylurea treatment required additional insulin therapy to achieve the therapeutic targets. Using U.K. Prospective Diabetes Study data, Holman (14) demonstrated a 4% decline per year of β-cell function in diet-, sulfonylurea-, or metformin-treated subjects.

This study evaluated the potential advantages of therapy with insulin alone in the earlier stages of evolution of the disease, as soon as combined oral hypoglycemic agents fail to maintain good metabolic control.

BENEFICIAL EFFECTS OF INSULIN

— To obtain adequate metabolic control, type 2 diabetic subjects often require high doses of insulin. In past years, a major barrier to the use of insulin was related to the perceived negative effect that high doses of the drug might have on insulin sensitivity. In an analysis of the reasons for underuse of insulin in type 2 diabetes in the U.S., this hypothesis was confuted by Riddle (15), who, on the basis of the results of three different major studies conducted in the middle 1980s, demonstrated that after insulin use, glucose disposal increased by 30–40% when compared with previous treatments.

Similar data were produced by Henry et al. (16) who showed that in type 2 diabetic patients on secondary failure of hypoglycemic oral agent therapy, a 6-month intensive insulin treatment significantly reduced the basal hepatic glucose output by 50% and increased the peripheral glucose uptake by 20%. Such improvement of insulin sensitivity corresponded to an amelioration of metabolic control, as in-

From the University of Perugia, Perugia, Italy.
Address correspondence and reprint requests to Massimo Massi-Benedetti, Department of Internal Medicine, University of Perugia, Via Enrico dal Pozzo, 06126 Perugia, Italy. E-mail: massi@unipg.it.
The authors of this article have no relevant duality of interest to declare.
This article is based on a presentation at the 1st World Congress of Controversies in Diabetes, Obesity and Hypertension (CODHy). The Congress and the publication of this article were made possible by unrestricted educational grants from MSD, Roche, sanofi-aventis, Novo Nordisk, Medtronic, LifeScan, World Wide, Eli Lilly, Keryx, Abbott, Novartis, Pfizer, Generx Biotechnology, Schering, and Johnson & Johnson.
DOI: 10.2337/dc08-s233

dicated by a reduction of both fasting and postprandial blood glucose that was maintained throughout the study period.

Severe hyperglycemia may induce peripheral insulin resistance. Pratipanawatr et al. (17) showed that normalization of blood glucose profiles by short-term insulin therapy in type 2 diabetic patients can reduce hyperglycemia-induced insulin resistance, as indicated by an improved insulin-stimulated glucose disposal.

Insulin treatment can also produce a beneficial effect on the insulin secretory capacity of the β-cell, as demonstrated in different studies in newly diagnosed type 2 diabetic subjects naive to pharmacological treatment (18,20). This same benefit of the efficacy of insulin in protecting the β-cell has not been confirmed in more advanced stages of the disease in subjects on hypoglycemic oral agent failure.

Cusi et al. (21) treated type 2 diabetic obese patients on secondary hypoglycemic oral agent failure with bedtime intermediate insulin alone over a period of 16 weeks. The subjects obtained a near-normalization of fasting plasma glucose and an overall improvement of the daily glycemic profile, although it was not possible to optimize postprandial control. The investigators also performed a clamp study before and after the 16-week insulin treatment that showed a significantly increased C-peptide secretion at the end of the study with respect to baseline.

Kawamori et al. (22) tested the effects on insulin secretion of three different insulin regimens in type 2 diabetic subjects with sulfonylureas failure. Meal-related insulin treatment, which normalized postprandial hyperglycemia, produced an increase of residual β-cell function. Improvement of β-cell function was further amplified by the basal-bolus approach, while a basal insulin supplement alone was not effective. The direct effect of insulin therapy on the β-cell was confirmed by the evidence that at the end of the study, the insulin requirement (units/day) in meal-related and basal-bolus regimens was lower with respect to insulin initiation, while no modification was seen in the case of basal insulin treatment.

These results suggest that a short-term period of meal-related insulin treatment, which can normalize postprandial hyperglycemia, increases residual β-cell function in type 2 diabetic subjects with secondary failure to long-term sulfonylurea therapy. The study also showed that while basal insulin supplement alone was not effective, the positive effect of a prandial insulin supplement could be further improved by a combined basal- and meal-related treatment program.

ADVERSE EFFECTS OF INSULIN TREATMENT — Obesity is one of the major determinants of insulin resistance. The risk of further weight gain in subjects who usually are already overweight or frankly obese may be considered a limiting factor for the initiation of treatment with insulin alone in type 2 diabetes. In fact, several experiences associated intensive insulin treatment with significant weight gain (23,24).

Two main issues should be taken into consideration. In some patients, weight gain is not the direct effect of insulin. Rather, it depends on the reduction of glycosuria determined by improved metabolic control with consequent reduction of energy waste (25).

The second issue is that interventional studies, such as the U.K. Prospective Diabetes Study, demonstrated that weight gain associated with intensive treatment does not produce negative cardiovascular effects (26).

Further concerns are related to the possible increased risk of hypoglycemic episodes in treating type 2 diabetic subjects with an insulin-only regime. However, Henry et al. (16) demonstrated that insulin treatment that produced a progressive improvement of metabolic control up to an average A1C of 5.1% was not necessarily associated with an unacceptable increased risk of hypoglycemia. In this study, the hypoglycemic episodes were concentrated in the early period of insulin treatment, mainly related to the process of insulin dose titration.

Moreover, in type 2 diabetes, insulin treatment is not usually associated with severe hypoglycemia, as observed in type 1 diabetes (27).

ADVERSE EFFECTS OF ORAL HYPOGLYCEMIC AGENTS — While insulin is effective in ameliorating metabolic control with positive effects on insulin sensitivity and secretion at an acceptable rate of adverse events, other studies address the potential negative effects of oral hypoglycemic agents on the β-cell, particularly sulfonylureas.

Rachman et al. (28) demonstrated that gliclazide was as effective as NPH insulin in controlling basal glucose concentrations in type 2 diabetic subjects who were not adequately controlled by diet alone, whereas both drugs were not successful in controlling postprandial excursions. Nevertheless, during sulfonylurea but not insulin treatment, a significant increase of postprandial levels of amylin and amylin-like peptide was observed. Thus, sulfonylureas might lead to increased disposition of islet amyloid, determining a faster decline in β-cell function.

More recently, Maedler et al. (29) found that in cultured human islets, acute exposure (4 h) to high doses of sulfonylureas induced β-cell apoptosis. The rate of β-cell death was increased and occurred at lower doses in cases of prolonged (4 days) contact, indicating a potential risk of long-term sulfonylurea therapy. On the other hand, sulfonylureas may produce negative effects not only on β-cell survival, but also on its function.

Ball et al. (30) demonstrated that prolonged exposure of β-cells to high doses of glibenclamide reduces the responsiveness of islets to successive stimulations by glibenclamide or tolbutamide. The inhibitory effect was reversed by a successive prolonged incubation without sulfonylureas, indicating a direct effect of glibenclamide on β-cell secretory capacity.

Pretreatment with sulfonylureas can also affect the β-cell response to high glucose. Del Guerra et al. (31) found that preincubation of human islets with glibenclamide or chlorpropamide reduced insulin release in response to acute glucose stimulation. In addition, in this study, a successive incubation with a sulfonylurea-free culture medium removed the inhibitory effect on β-cell secretion.

New oral drugs may have lesser adverse effects on β-cell function. Various studies have demonstrated the positive effects of glitazones on β-cell function (32–35). In addition, glitazones ameliorate sensitivity of skeletal muscle, adipose tissue, and hepatocytes to circulating insulin. Several reports demonstrated that glitazones in combination with insulin effectively improved metabolic control with a concomitant reduction of total daily insulin dose (36–39). However, their use in combination with insulin is still not allowed in several countries because of the increased risk of fluid retention. In fact, glitazones have been significantly associated with an increased risk of edema and anemia in people treated with these drugs (36–38,40). Several authors indicated an important anti-natriuretic effect of insulin causing possible fluid retention and

plasma volume expansion (41). In a comparative study where rosiglitazone was combined with insulin (42), patients in the combination arm showed a marked weight gain and a higher prevalence of edema with respect to the rosiglitazone-alone arm.

In the 2004 ADA consensus document on glitazone use in type 2 diabetes with regard to fluid retention and heart failure (43), the list of risk factors for heart failure during glitazone treatment comprises several conditions common in type 2 diabetic patients, such as hypertension, advanced age, and long-lasting diabetes, and particularly specifies the insulin co-administration.

Finally, concerns exist on the negative effects of sulfonylureas on myocardial function, especially during ischemic conditions. Glibenclamide treatment affects ischemic preconditioning, exposing a possible higher risk of cardiovascular mortality in sulfonylurea-treated type 2 diabetic patients with myocardial infarction (44). In addition, myocardial function during ischemic challenge was found to be altered to a higher degree in glibenclamide-treated compared with insulin-treated type 2 diabetic subjects (45).

USING INSULIN ALONE IN TYPE 2 DIABETES

— Despite the fact that the efficacy of treatment with insulin alone in type 2 diabetes, in terms of glycemic control improvement and also protection of the β-cell function, has been supported by many studies, this therapeutic approach is widely underused.

The National Health and Nutrition Examination Survey showed a decline between the years 1988–1994 and 1999–2000 in the percentage of type 2 diabetic patients using treatment with insulin alone, which was accompanied by a concomitant increase of combination therapy (46). Contrasting to common guidelines that call for ever tighter glycemic control, the comparison of the two periods demonstrated that a lower proportion of subjects achieved the desirable glycemic targets in the years 1999–2000, suggesting inappropriate treatment.

Furthermore, the introduction of rapid-acting analogs has also been associated with better control of postprandial excursions in type 2 diabetic patients (47,48).

Different authors highlighted the important role of postprandial hyperglycemia on the development of macrovascular complications (49–51). Ceriello (52) showed that postload hyperglycemia determines overproduction of superoxide in the mitochondria and that this is the initial step in the activation of all the other pathways involved in the pathogenesis of diabetes complications.

Bonora et al. (53) demonstrated that postprandial hyperglycemia is also a frequent event in type 2 diabetic subjects usually considered well controlled. This evidence, combined with the findings on the role of hyperglycemia on cardiovascular complications, may support the opportunity to adequately control postprandial excursions in type 2 diabetes with earlier intensive insulin therapy.

Some authors might argue that tight glycemic control may be reached with combination therapy; however, different studies have demonstrated that increasing the complexity of the treatment may lead to poor compliance and management errors.

Mateo et al. (54) demonstrated that the daily number of pills is the major predictor of nonadherence to one or more drugs in multifactorial treatment in type 2 diabetic patients.

In a study conducted on type 2 diabetic patients treated with sulfonylureas alone, the recommendation of three or more tablets per day was associated with a 50% less adherence to the prescription (55).

As an obvious consequence, poor adherence and management errors are usually associated with inadequate metabolic control and increased risk of adverse effects. In a diabetic population, Pladeval et al. (56) have shown that the nonadherents to hypoglycemic treatments have significantly higher levels of A1C than people with better compliance.

SUMMARY

- Insulin therapy has beneficial effects on β-cell survival and function and on peripheral insulin sensitivity.
- Basal-bolus insulin regimens seem to amplify the positive effects on insulin sensitivity.
- Several studies highlight the potential negative effects of a number of sulfonylureas on the β-cell.
- Glitazones, despite their positive effect on the β-cell and efficacy in ameliorating metabolic control when associated with insulin, might produce an increased risk of fluid retention.
- A number of studies have confirmed the safety of insulin therapy in type 2 diabetes with regard to both the risk of weight gain and hypoglycemia.
- In conclusion, sufficient evidence on pathophysiological, clinical, and safety aspects are available to indicate that therapy with insulin alone in type 2 diabetic subjects in case of failure of oral agents may be a better option when compared with combined therapy.

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