Combined Therapy With Insulin Plus Oral Agents: Is There Any Advantage?

An argument in favor

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Physicians in many countries use combinations of antihyperglycemic agents to achieve the best glycemic control possible under the conditions faced by individual patients with type 2 diabetes. This widespread use of combined therapies, including oral agents combined with insulin, suggests that the diabetes community accepts the value of this tactic. A routine need for combined therapies was explicitly acknowledged by the investigators in the U.K. Prospective Diabetes Study. Review of the results of 9 years of monotherapy with various agents in the U.K. Prospective Diabetes Study found that fasting plasma glucose (FPG) was kept below 7.8 mmol/l (140 mg/dl) in only 18% of participants using metformin, 24% using a sulfonylurea, and 42% using insulin (1). Corresponding values for keeping A1C below 7% were 13% with metformin, 24% with a sulfonylurea, and 28% with insulin. Regardless of which agent was used as initial therapy, a progressive worsening of glycemic control ensued, largely because of a gradual decline of endogenous insulin production. A substudy embedded in the U.K. Prospective Diabetes Study compared early addition of basal insulin to a sulfonylurea with insulin alone and showed that over 6 years of treatment the combined regimen achieved lower median A1C (6.6 vs. 7.1%) and also less major hypoglycemia (1.6 vs. 3.2% annually) (2). The U.K. Prospective Diabetes Study investigators concluded that "the majority of patients need multiple therapies to attain these glycemic targets in the longer term" (1).

However, combined therapy with oral agents and insulin has not been accepted as desirable by all experts. This article describes an argument in favor of combined therapy in a recent debate examining the advantages and limitations of this approach. Because reports of various combined regimens have been summarized previously, consistently showing better glycemic control with combined therapy (3–6), this article will not systematically review all published studies. Instead, it will describe the pharmacologic rationale for combining agents generally, present some new physiologic evidence for combining an oral agent with insulin, and offer a few examples of clinical studies showing advantages of combined therapy over insulin used alone.

PHARMACOLOGIC RATIONALE FOR COMBINED THERAPY

— The main benefit of using antihyperglycemic agents together is a better ratio of desired to undesired effects. Figure 1*A* shows typical patterns of therapeutic effects and unwanted effects with pharmacotherapies (7). Whereas most of the desired effect occurs well short of the maximal recommended dosage of most agents, the side effects generally are uncommon and minor at lower dosage and much more frequent and prominent at full dosage. Figure 1*B* and *C* show, respectively, similar patterns for a biguanide (metformin) and a sulfonylurea (glimepiride) based on published data (8,9). Metformin's mean ability to control A1C increases almost linearly to a dosage of ~2,000 mg daily and then seems to decline at 2,500 mg. Side effects, in contrast, occur in ~5% of patients at 500 mg daily, but at 2,500 mg, are reported by at least 25%. The apparent decline of metformin's effectiveness at higher dosages may be related to frequent omission of doses due to such side effects. Glimepiride's main side effect, hypoglycemia, occurs mainly at higher dosages as well, while lower dosages provide near-maximal improvement of A1C.

Important principles emerge from this kind of information. Greater therapeutic power can be achieved by combining two or more agents with different mechanisms of action. A second agent logically may be added when mid-range dosage of the first agent is no longer fully effective, to obtain the greatest benefit from the added cost and effort. Moreover, if antihyperglycemic agents are not routinely increased to maximal dosage, side effects should be much less common.

These principles are relevant to insulin as well. Figure 2 shows the relationship between achieved A1C and the frequency of hypoglycemia, the limiting side effect of insulin therapy (10). In this study, treatment with two injections of human NPH insulin was compared with two injections of insulin detemir, each used in combination with one or more oral antihyperglycemic agents. Both regimens showed increasing hypoglycemia when A1C approached 7%, suggesting that a further increase of insulin dosage is often unwise and other tactics should be considered. Among such tactics might be use of a less hypoglycemia-prone long-acting insulin analog (glargine or detemir) in preference to human NPH (10,11). Also, control might be improved without greater risk of hypoglycemia by addition of prandial insulin doses (another form of combined therapy) or addition of another oral agent (as will be discussed later). Despite the nearly unlimited glucose-lowering power of insulin, minimizing of

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Abbreviations: FPG, fasting plasma glucose.

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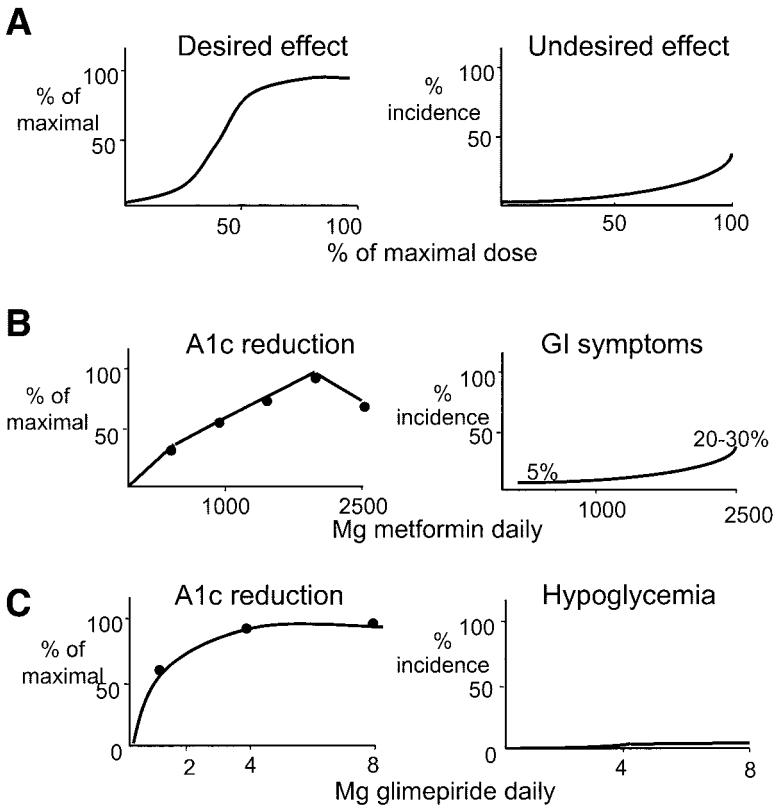

Figure 1—*Relationships between dosages and effects of medications, illustrating the principle that submaximal dosages provide significant desired effects while limiting undesired effects. A shows theoretical curves for medications generally. B and C show data adapted from published dose-ranging studies of metformin (8) and glimepiride (9), respectively. GI, gastrointestinal.*

the risk of hypoglycemia depends on timely use of combined therapies.

PHYSIOLOGIC ASPECTS OF COMBINED THERAPY

— The ability of oral agents to reduce risk of insulin-induced hypoglycemia at a given level of glycemic control depends mainly on enhancing the effects of endogenous insulin. Normally, increments of plasma glucose are reduced by appropriate increases of endogenous insulin secretion, and decrements of glucose lead to decreased secretion (12). This normal buffering action is reduced when endogenous secretion is impaired, leading to increased glycemic variability. Although endogenous insulin is impaired in all patients with type 2 diabetes requiring insulin, it is rarely entirely absent. Therefore, oral agents can enhance glycemic buffering by potentiating either the secretion or the action of remaining endogenous insulin.

This process is most apparent in the case of insulin-sensitizing agents. Metformin acts mainly by enhancing the responsiveness of the liver to insulin, controlling hepatic glucose production while fasting (13). Thiazolidinediones improve the insulin responsiveness of both the liver and peripheral tissues and thereby have desirable effects on both fasting glucose and postprandial glucose disposal (14). When used together with injected insulin, both classes of agents should enhance the buffering effect of secreted insulin. How this might occur is illustrated by a physiologic study (15) of 20 patients with type 2 diabetes who received 4 weeks of basal-bolus treatment with insulin infusion pumps followed by addition of either metformin or the thiazolidinedione troglitazone (which is no longer used because of hepatic toxicity) (Fig. 3). Nearly normal glycemic patterns were achieved with very intensive use of insulin alone and maintained after the addition of either oral agent. The dosage of injected insulin needed to maintain control decreased by 31% when metformin was added and 53% when troglitazone was added. The 24-h profiles of both glucose and C-peptide remained the same with addition of either metformin or the thiazolidinedione. Because the C-peptide profiles (which reflect the secretion of endogenous insulin) were unchanged, a greater proportion of insulin effect must have been provided by the more normally regulated endogenous insulin secretion. Of course, the actions of injected insulin are also increased by an insulin-sensitizing oral agent, and this contributes to the reduction of dosage needed. A smaller subcutaneous depot of insulin may also lead to fewer tendencies for exercise to result in inappropriately increased absorption of insulin. These observations

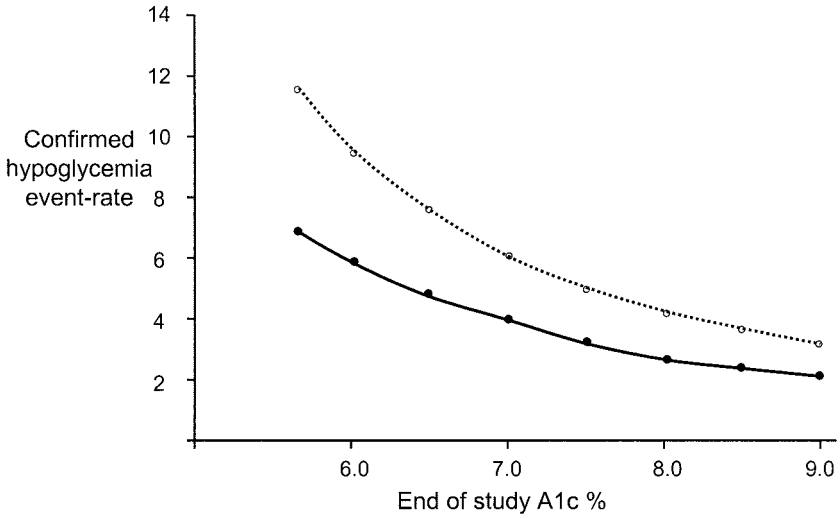

Figure 2—*Modeled regression curves showing the relationship between rates of hypoglycemia and achieved glycemic control reflected by A1C values during treatment of patients with type 2 diabetes with human NPH insulin (○) or insulin detemir (●). The curves illustrate that achievement of excellent glycemic control may be limited by increasing risk of hypoglycemia. Adapted with permission from Hermansen et al. (10).*

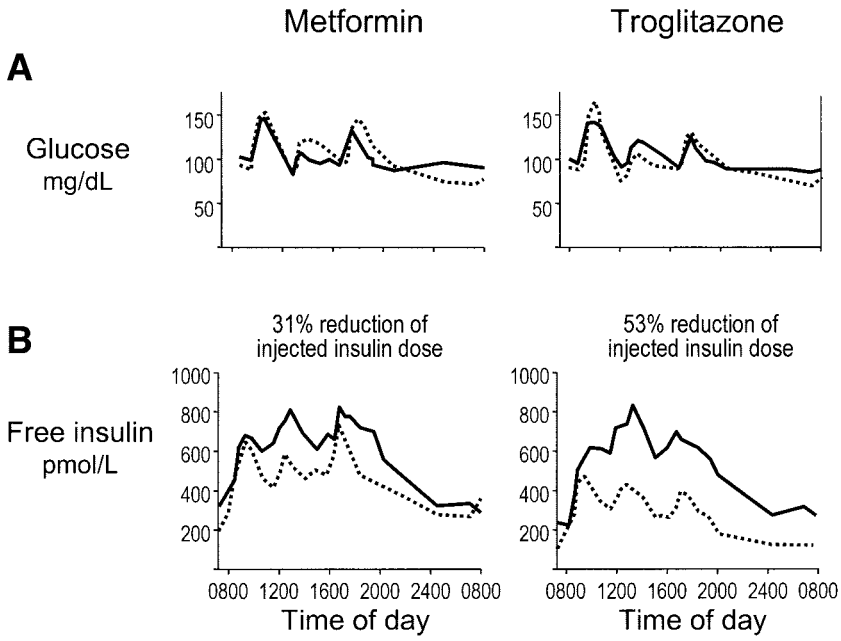

Figure 3—*Twenty-four-hour patterns of plasma glucose* (A, *above*) *and serum insulin* (B, *below*), *during intensive treatment of type 2 diabetes. Sequential studies during continuous subcutaneous insulin infusion without (solid lines) and with (broken lines) concurrent treatment with metformin or troglitazone are shown. Adapted with permission from Yu et al. (15).*

lead to the prediction that continuing an insulin sensitizer when insulin is started may permit equal glycemic control with less risk of hypoglycemia compared with using insulin alone, or else better glycemic control without increased hypoglycemia. Evidence supporting this prediction will be presented later.

How sulfonylureas and other agents potentiating insulin secretion may be helpful in combination with insulin is less obvious. For many years, it was assumed that injected insulin could be provided in sufficient quantity and with adequate timing to maintain excellent glycemic control of most patients with type 2 diabetes. Wide clinical experience has shown this assumption is not generally true, and hypoglycemia is a leading problem with intensive insulin treatment in type 2 as in type 1 diabetes. Consequently, various studies have tested the effects of combining sulfonylureas as well as metformin with insulin. Yki-Jarvinen (4) has summarized the results of a number of such studies examining patients whose prior oral therapy was or was not continued when insulin treatment was started. In this analysis, the mean final insulin dosage was 32% lower when metformin was continued, 42% lower when a sulfonylurea was continued, and 62% lower when both oral agents were continued. The significantly lower need for injected insulin with continuation of sulfonylureas suggests that these agents, like metformin and thiazolidinediones, have the potential to enhance the stabilizing effects of remaining endogenous insulin.

A physiologic study by our group reported previously in preliminary form lends support to this concept (16). Ten patients with type 2 diabetes previously taking a sulfonylurea (mean ± SE age 50 ± 3 years, duration of diabetes 5 ± 1 years, BMI 34 ± 3 kg/m^2) were studied in a randomized unmasked crossover study. Prior sulfonylurea treatment was stopped and replaced with either 5 mg glyburide (Micronase, Upjohn) before both breakfast and the evening meal or no oral therapy. At the same time, all participants began taking human 70/30 (70% NPH/30% regular) insulin (Novolin) before the evening meal. Insulin dosage was titrated to achieve FPG of ~7.8 mmol/l (140 mg/dl). After insulin dosage and glucose had been stable for at least 2 weeks, each participant entered the clinical research center for a 24-h profile day followed by a fasting exercise study on the second day. When these were completed, each participant crossed over to the alternate oral treatment (glyburide or no glyburide) with continued titration of once-daily 70/30 insulin to maintain FPG at ~7.8 mmol/l for at least 2 weeks before restudy. Twice as much injected insulin was needed to reach this level of control (66 ± 12 units daily with insulin alone vs. 34 ± 5 units with insulin plus glyburide). The profiles of glucose, free insulin, and C-peptide are shown in Fig. 4. Mean FPG was the same (7.5 ± 0.2 and 7.3 ± 0.2 mmol/l) with and without glyburide, and the 24-h profiles were similar except for modest but statistically significant elevations in mid-afternoon and before and after the evening meal when glyburide was not taken. Free insulin levels were not statistically different between treatments except for slightly higher levels in the mid-afternoon with glyburide. However, C-peptide levels were about twice as great during glyburide treatment at the fasting measurement, and this difference continued throughout the 24-h period. These patterns confirm that endogenous insulin contributes more to glycemic control with combined therapy than during treatment with injected insulin alone.

For the exercise study on the second day of each admission, the morning dose of glyburide and breakfast were omitted and the participants exercised on a resistance bicycle at 25% of previously measured maximal exercise capacity for three 25-min periods separated by 5-min rest periods for blood collection (Fig. 5). When glyburide had been taken (except the morning of the study), glucose changed little during and after exercise. When insulin was used alone, glucose declined from baseline during exercise and was just starting to increase again 2 h after exercise ended. The mean between-treatment difference ranged from 1.1 to 1.9 mmol/l (20 to 34 mg/dl) during and after exercise. Fasting free insulin values were similar at baseline and from this level increased ~5% during exercise when insulin was used alone. When glyburide was used, mean free insulin decreased ~10% during exercise and showed a normal postexercise increase.

This small study suggests that plasma levels of glucose are less likely to decline inappropriately during fasting and exercise when a sulfonylurea is used together with insulin than with insulin alone, most likely because changes of plasma insulin are more appropriate. Had FPG been normal (<5.6 mmol/l [100 mg/dl]) when exercise began, some participants likely would have had hypoglycemic symptoms during exercise with insulin alone, but not with combined therapy.

Greater stability of FPG levels during combined insulin-sulfonylurea therapy was also seen in two other studies done by

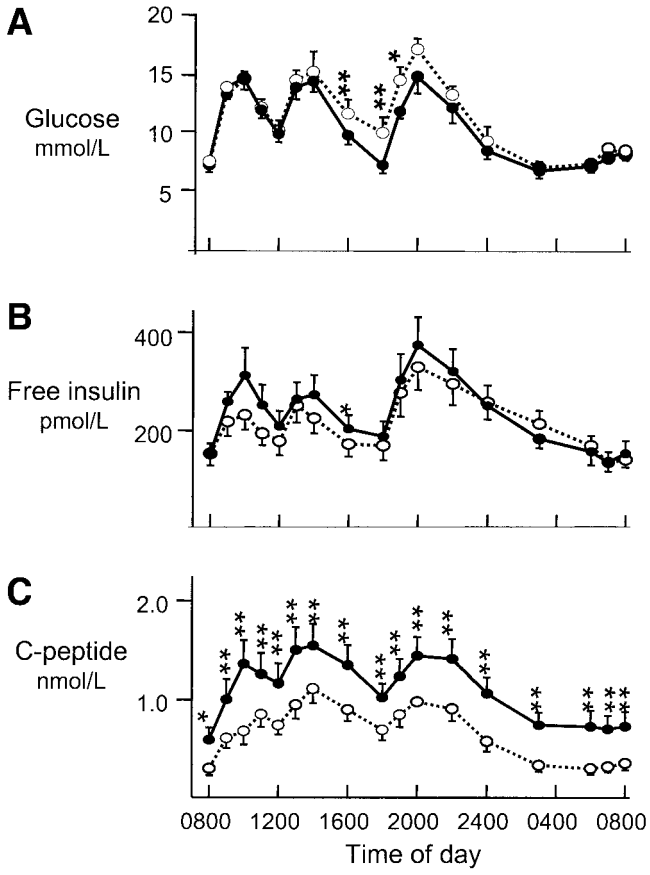

Figure 4—*The 24-h patterns of plasma glucose* (A)*, serum insulin* (B)*, and serum C-peptide* (C) *during treatment of type 2 diabetes with human 70/30 insulin before supper. Sequential studies during insulin therapy alone* (○) *and insulin plus glyburide* (●) *are shown. Data previously reported as abstract by Riddle et al. (17).* *$P < 0.05$; **$P < 0.01$.

our group, as assessed by the means of SD of sequential FPG values for individual patients toward the end of these studies when insulin dosage was stable. In one, the mean SD (± SE) was 1.7 ± 0.2 mmol/l during treatment with bedtime NPH insulin alone vs. 1.1 ± 0.1 with NPH plus glyburide (33% lower) (17). In the other, the mean SD was 1.4 ± 0.3 mmol/l when human 70/30 insulin alone was taken before the evening meal vs. 0.8 ± 0.1 with 70/30 plus glyburide (43% lower) (18).

A major limitation of these older studies was the use of glyburide. This drug has been shown to cause more hypoglycemia than other widely used sulfonylureas, presumably through a greater tendency to provoke insulin secretion independent of current glucose concentrations (19). In addition, it interferes with cardiac ischemic preconditioning, whereas glimepiride, glipizide, and gliclazide do not (20,21). Perhaps related to this effect, some studies suggest glyburide is associated with higher mortality rates than other secretagogues (22). Had this study been done with a longer-acting yet less hypoglycemia-prone secretagogue, such as glimepiride or glipizide-GITS (gastrointestinal therapeutic system), similar or better results might have been observed, and they could more confidently be generalized to current clinical practice.

SELECTED CLINICAL TRIALS ILLUSTRATING POTENTIAL BENEFITS

— Clinical studies have confirmed that glycemic control can be improved when oral agents are continued when insulin is started, or added to established insulin treatment (4,5). However, many were limited by lack of systematic titration of insulin dosage to demonstrate the full potential of the regimens tested. Studies in which insulin titration was more aggressive show the benefits of combined therapy more clearly. For example, in one small randomized study, prior therapy with glipizide, 10 mg twice daily, was continued or stopped when bedtime human NPH insulin was started, and NPH dosage was increased, systematically seeking FPG 6.7 mmol/l (120 mg/dl) (23). With NPH alone, the final mean FPG was 7.8 mmol/l (140 mg/dl) and A1C was 7.8%, while continuation of glipizide allowed mean FPG to be reduced to 6.3 mmol/l (113 mg/dl) and A1C to 7.1%. In another study, patients previously treated with NPH and regular human insulin were randomized to addition of placebo or metformin followed by intensification of multiple-injection therapy with the same insulins (24). After 6 months, intensified insulin plus placebo improved A1C from 9.1 to 7.6% but increased weight by 3.2 kg. In contrast, intensification of insulin with addition of metformin reduced A1C from 9.0 to 6.5%, while weight increased just 0.5 kg. In both of these studies, the rates of hypoglycemia were similar between treatments.

Perhaps the best demonstration of the advantage of combining an oral agent with insulin to date appears in an interim analysis from a study designed to test whether metformin combined with insulin will reduce cardiovascular morbidity compared with insulin alone (25). A total of 390 patients who were already taking insulin (with or without metformin) were randomized to management with two to four injections of insulin plus either placebo or metformin for a 16-week active treatment phase. The authors reported "unexpected favorable effects of metformin" during this period. More participants dropped out of the metformin arm (25 vs. 12), but for those completing 16 weeks, the mean A1C was 7.6% with insulin and placebo vs. 6.9% with combined therapy. Weight increased 1.2 kg with insulin and placebo, but decreased 0.4 kg with combined therapy. Despite 0.6–0.7% lower A1C, hypoglycemia was no more frequent with combined therapy.

Results of 4 years of follow-up in this study have recently been reported in preliminary form (26). Better glycemic control was still present in the combined therapy arm (A1C 0.4% lower, $P < 0.001$), and the weight increase versus placebo was 3.07 kg less ($P < 0.001$). The primary composite medical end point (microvascular events, macrovascular events, sudden death) showed a statistically insignificantly lower hazard ratio (0.92, $P = 0.34$), but the secondary (macrovascular) end point showed 39% lower risk with combined therapy (hazard ratio 0.61, $P < 0.02$).

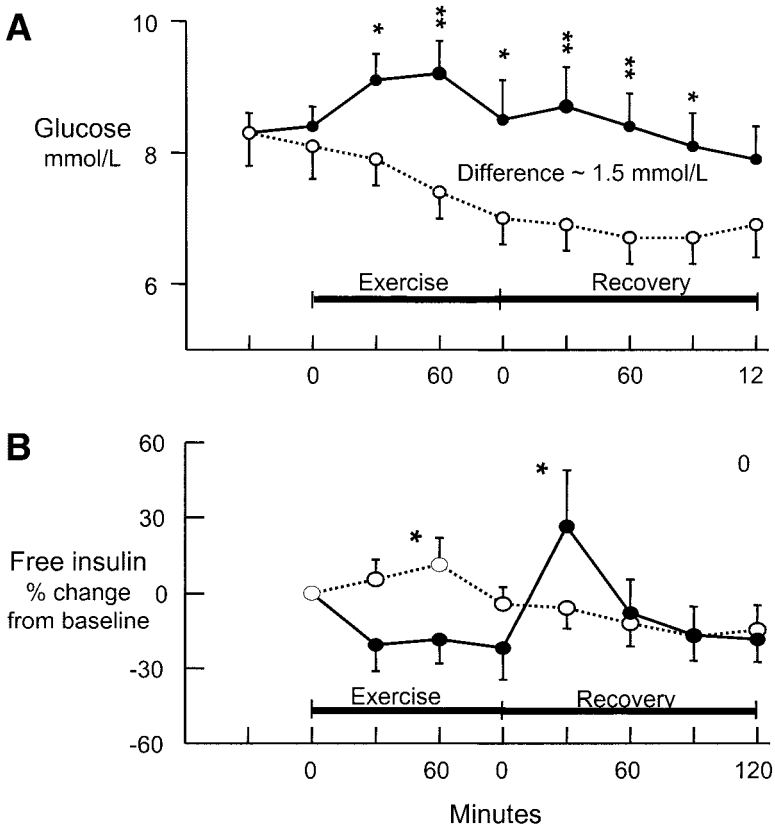

Figure 5—*Patterns of plasma glucose* (A) *and serum insulin* (B) *in type 2 diabetes, during and after 90 min exercise while fasting. Sequential studies compared treatment with 70/30 insulin before supper alone* (○) *or with insulin combined with glyburide* (●). *Data previously reported as abstract by Riddle et al. (17).* $*P < 0.05$; $**P < 0.01$.

UNANSWERED QUESTIONS

Many questions about the value of combining other antihyperglycemic agents with insulin remain. Notable among them is whether metformin or thiazolidinediones, when used with insulin, will reduce long-term risks of cardiovascular events, as has been postulated. The preliminary results with metformin cited above are very encouraging, but recent analyses of medical outcomes with pioglitazone (27) and rosiglitazone (28) treatment, including when combined with insulin, suggest caution with this combination. Briefly, congestive heart failure in susceptible individuals occurs more often when thiazolidinediones are used, especially with insulin, and the possibility that risk of myocardial infarction may be increased by thiazolidinediones is under discussion. Ongoing trials, including Action to Control Cardiovascular Risk in Diabetes (ACCORD) and the Veterans Affairs Diabetes Trial (VADT), may further clarify the potential risks and benefits of combining insulin with other agents.

In addition, the recent or impending arrival of newer agents such as the rapid-acting secretagogues (repaglinide and nateglinide), an amylin analog (pramlintide), agonists of the glucagon-like peptide 1 receptor (exenatide, liraglutide, and others), and the dipeptidyl-peptidase 4 inhibitors (sitagliptin, vildagliptin, and others) adds to the options for combined therapy. Use of all these agents with insulin is supported by good physiologic principles, but adequate studies remain to be done.

SUMMARY

Combined therapy with insulin plus oral agents is widely used and has been shown to be effective in improving glycemic control in many short-term studies. The rationale for using combined regimens to minimize the dosage of antihyperglycemic agents and thereby their unwanted effects (hypoglycemia in the case of insulin) is clear. When oral therapy is continued during insulin therapy, enhancing either the availability or effectiveness of endogenous insulin, glycemic stability may improve and may lead to better glycemic control with similar hypoglycemic risk, or equal glycemic control with less hypoglycemia. In the case of metformin, combination with insulin also limits the risk of weight gain. However, only a few physiologic studies clarifying the mechanisms underlying these benefits are available, and longer-term medical outcome studies comparing insulin alone with insulin plus oral therapy are lacking. Evidence that insulin-metformin therapy can provide better glycemic control with less risk of hypoglycemia and little weight gain, compared with insulin alone, supports this combination as a standard method of treating type 2 diabetes to usual glycemic targets.

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