

# Guidelines for Premeal Insulin Dose Reduction for Postprandial Exercise of Different Intensities and Durations in Type 1 Diabetic Subjects Treated Intensively With a Basal-Bolus Insulin Regimen (Ultralente-Lispro)

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**OBJECTIVE** — To evaluate and validate appropriate premeal insulin dose reductions for postprandial exercises of different intensities and durations to minimize the risk of exercise-induced hypoglycemia in type 1 diabetic subjects.

**RESEARCH DESIGN AND METHODS** — Eight male type 1 diabetic patients on a basal-bolus insulin regimen of ultralente (UL) as basal insulin and lispro (LP) as premeal insulin were tested in a randomized, crossover fashion during postprandial exercise at 25%  $\text{VO}_{2\text{max}}$  for 60 min, 50%  $\text{VO}_{2\text{max}}$  for 30 and 60 min, and 75%  $\text{VO}_{2\text{max}}$  for 30 min starting 90 min after a standardized mixed breakfast (600 kcal, 75 g carbohydrates). Each subject served as his own control and was tested after a full dose of insulin LP (LP 100%) and/or 50% (LP 50%) and/or 25% (LP 25%) of the current dose.

**RESULTS** — At all intensities, the full premeal insulin dose was associated with an increased risk of hypoglycemia. At 25%  $\text{VO}_{2\text{max}}$  for 60 min, a 50% reduction in the premeal insulin dose resulted in plasma glucose of  $-0.62$  mmol/l compared with baseline at the end of exercise. At 50%  $\text{VO}_{2\text{max}}$  for 30 and 60 min, 50 and 75% reductions of the premeal insulin dose were associated with plasma glucose of  $-0.39$  and  $+0.49$  mmol/l, respectively, at the end of the exercise. At 75%  $\text{VO}_{2\text{max}}$ , a 75% reduction of the premeal insulin dose was required to achieve appropriate postexercise plasma glucose ( $+0.71$  mmol/l). Such reductions in the premeal insulin dose resulted in a 75% decrease in the incidence of exercise-induced hypoglycemia.

**CONCLUSIONS** — In well-controlled type 1 diabetic subjects on intensive insulin therapy with the basal-bolus (UL-LP) insulin regimen, risk of hypoglycemia can be minimized during postprandial exercises of different intensities and different durations by appropriate reduction of premeal insulin LP.

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Although exercise is not considered part of the treatment of type 1 diabetes, the American Diabetes Association recently reemphasized the necessity of developing strategies that

would allow type 1 diabetic subjects to participate safely in physical activities according to their desires and goals. While no beneficial effect of exercise on glycemic control has been demonstrated in

type 1 diabetic patients (1), it is believed that they could profit from regular exercise in terms of cardiovascular fitness, social integration, or simply recreation (2). However, a major problem still persists for type 1 diabetic subjects performing physical exercise: the long-recognized risk of hypoglycemia during and after exercise.

Despite abundant literature on diabetes and exercise (3–9), there are scant data regarding the formulation of guidelines for exercise of different intensities and of different durations by type 1 diabetic patients. Nevertheless, the American Diabetes Association clearly states that these patients can get involved in any kind of exercise as long as they are well controlled and are able to adjust their therapeutic regimens accordingly. The basal-bolus insulin regimen with ultralente (UL) as basal insulin and insulin lispro (LP) as the premeal insulin does offer some advantages for those who want to undertake postprandial exercise. Insulin LP is absorbed much faster than regular insulin and, therefore, improves the early postprandial glycemic increase and reduces the incidence of late postprandial hypoglycemia (10–12). More recently, we showed that for type 1 diabetic subjects on a basal-bolus regimen, premeal insulin LP was better suited than regular insulin for postprandial exercise (13).

The present study was designed to validate, in type 1 diabetic subjects on a basal-bolus insulin regimen (UL-LP), the appropriate premeal insulin LP dose reduction for postprandial exercise of different intensities (25, 50, and 75% maximum aerobic capacity [ $\text{VO}_{2\text{max}}$ ]) and different durations (30 and 60 min) to minimize the risk of hypoglycemia during and after exercise.

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**Abbreviations:** ANOVA, analysis of variance; CHO, carbohydrate; CV, coefficient of variation; LP, lispro; UL, ultralente.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

## RESEARCH DESIGN AND METHODS

Eight male well-controlled type 1 diabetic subjects participated in this study. Female subjects were not invited to participate because of the profound effect of menstrual cyclicity on glucose homeostasis (14). The mean age was  $33.0 \pm 3.1$  years, BMI was  $23.4 \pm 0.6$  kg/m<sup>2</sup>, duration of diabetes was  $12.6 \pm 3.1$  years, and  $\dot{V}O_{2\max}$  was  $37.8 \pm 3.5$  ml · kg<sup>-1</sup> · min<sup>-1</sup>. All patients were on the basal-bolus insulin regimen using insulin LP before each meal and UL at bedtime as basal insulin (insulins were kindly provided by Eli Lilly Canada Inc., Scarborough, Ontario, Canada). They had no significant diabetic complications, and insulin was the only current medication. This protocol was approved by the institutional scientific and ethics committees, and all patients gave their informed consent.

All subjects were familiar with carbohydrate (CHO) counting and with the adjustment of their insulin doses according to specific algorithms as described previously (15,16). Premeal insulin LP (mean prebreakfast dose was  $1.1 \pm 0.19$  U/10 g of CHO) was always injected immediately before the meal in the abdomen. UL was given at bedtime (mean dose was  $28.3 \pm 5.5$  U) in the same region (thigh, buttock, or arm) throughout the study. They were all well controlled with a mean HbA<sub>1c</sub> of  $6.1 \pm 0.002\%$  (normal 3.5–5.7%).

The subjects were submitted to the following experimental protocols in a randomized, crossover fashion: 1) postprandial rest after a full dose of insulin LP (LP 100%); 2) postprandial exercise at 25%  $\dot{V}O_{2\max}$  for 60 min, a) after LP 100% and b) after 50% of the insulin LP dose (LP 50%); 3) postprandial exercise at 50%  $\dot{V}O_{2\max}$  for 30 min, a) after LP 100% and b) after LP 50%; 4) postprandial exercise at 50%  $\dot{V}O_{2\max}$  for 60 min, a) after LP 100%, b) after LP 50%, and c) after 25% of the insulin LP dose (LP 25%); 5) postprandial exercise at 75%  $\dot{V}O_{2\max}$  for 30 min, a) after LP 100% and b) after LP 25%. Within each experimental exercising protocol, the duration and intensity of the exercise as well as the premeal insulin dose reduction were randomized. Pre-meal insulin dose reduction was considered appropriate if the plasma glucose reached at the end of the exercise period was similar or close to the premeal level. Hypoglycemia was defined as plasma glucose below 3.5 mmol/l. It was considered severe if the subject was confused and re-

quired assistance from another person; otherwise, it was considered minor hypoglycemia.

All eight subjects were studied at rest. Six subjects participated in each set of exercise protocols of the same intensity and duration at various LP doses; therefore, each patient always served as his own control. Five of the eight subjects participated in all experimental protocols. For all protocols, the patients were comparable in terms of age, BMI, duration of diabetes, and glycemic control.

Each experiment was started at 7:30 A.M. after an overnight fast. After two baseline samplings, the patients injected their prebreakfast insulin LP (LP 100% =  $8.5 \pm 1.4$  U, LP 50% =  $4.4 \pm 0.7$  U, LP 25% =  $3.0 \pm 0.5$  U), which, when expressed in U/10 g CHO, did not change significantly throughout the study. A standard breakfast consisting of bread, margarine, one egg, and herbal tea (600 kcal, 75 g CHO) was ingested over 15 min immediately after the premeal insulin injection. For the resting protocol, the subjects remained seated during the entire experiment (180 min). For the exercise protocols, they were submitted to 30- or 60-min cycle ergometer exercise at 25, 50, or 75%  $\dot{V}O_{2\max}$  90 min after the beginning of the meal. They were then followed for 1 h postexercise during recovery. Therefore, the overall duration of the exercise experiment was 180 or 210 min, depending on the duration of the exercise (30 or 60 min). Capillary blood glucose was monitored intensively for 18 h postexperiment; at least six measurements were recorded. During this period, the subjects were asked to maintain their usual insulin doses, physical activities, and dietary habits. During the experiment, venous blood samples were drawn at 10- to 15-min intervals for the measurement of plasma glucose, free plasma insulin, and plasma glucagon. Plasma glucose was determined immediately after sampling by the glucose oxydase method (Beckman Instruments, Fullerton, CA). If the plasma glucose level was lower than 3.5 mmol/l, or lower than 4 mmol/l with hypoglycemic symptoms, dextrose 20% was infused to maintain plasma glucose over 3.5 or 4.0 mmol/l. Free plasma insulin was measured with a radioimmunoassay kit (Immunocorp Science, Montreal, PQ, Canada) in which the dilution curves for regular insulin and insulin LP were virtually superimposable. The 3,500-kDa

active subfraction of glucagon was determined by radioimmunoassay (Diagnostic Products, Los Angeles, CA) after polyethylene glycol precipitation.

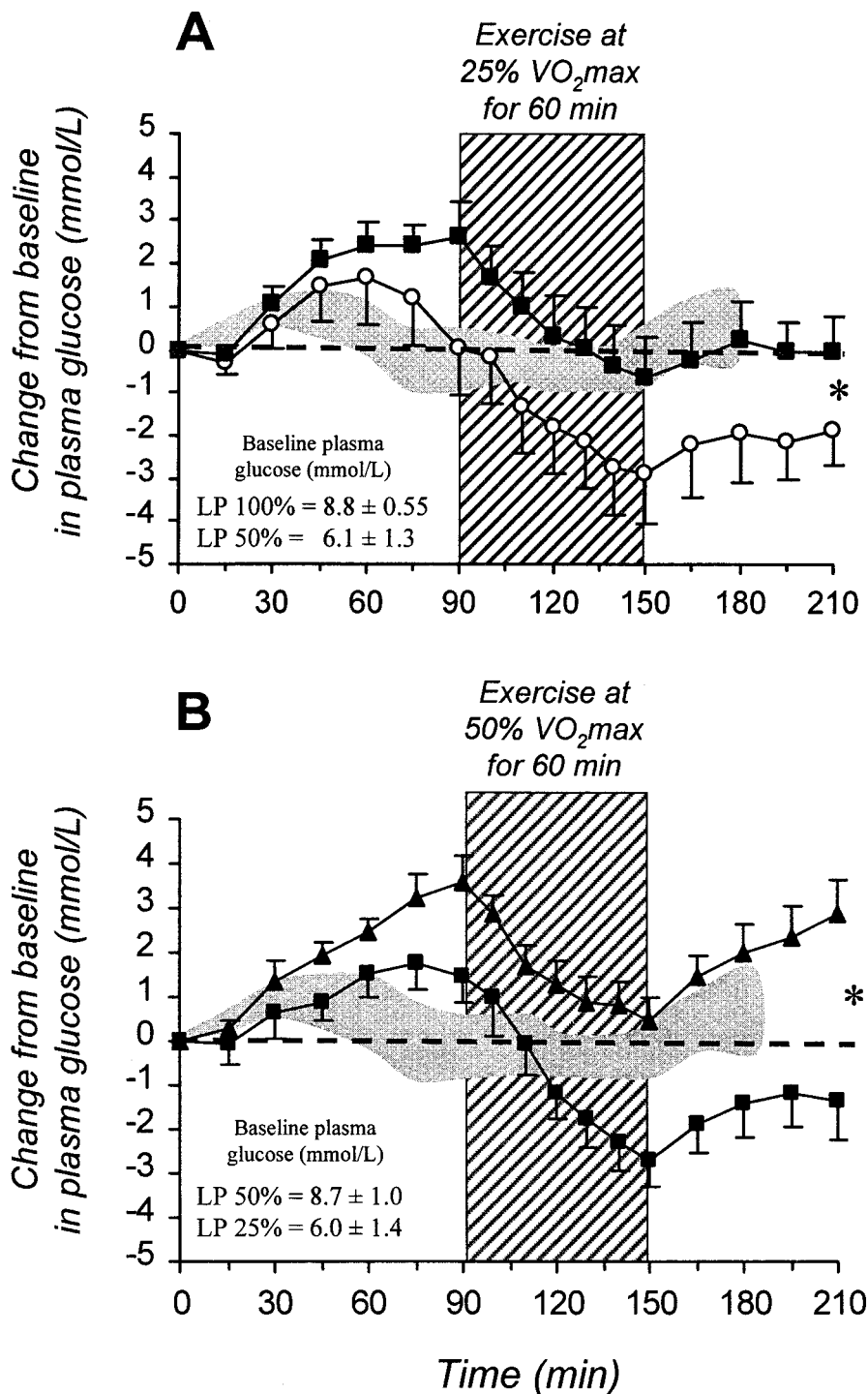
The data were assessed by analysis of variance (ANOVA) for repeated measures with the paired or unpaired Student's *t* test, Wilcoxon's rank-sum test for paired data, or Friedman's repeated measures by ANOVA on ranks when applicable (SigmaStat, version 2; Jandel, San Rafael, CA). These data are given as means  $\pm$  SEM.

**RESULTS** — Overall, 60 metabolic experiments were conducted. Whether data with or without glucose infusion for hypoglycemia were included did not modify the statistical analysis. For the final analysis, however, these values were included.

Mean fasting plasma glucose before the standardized breakfast was  $7.98 \pm 0.49$  mmol/l (range 4.2–11.4, coefficient of variation [CV] 47%) with no significant difference between the various experimental protocols (Figs. 1 and 2). When the subjects were studied at rest, they injected their full dose of the current premeal insulin LP (LP 100%) just before the standardized breakfast. In the early postprandial period, plasma glucose peaked at  $0.8 \pm 0.32$  mmol/l over baseline at 30 min after the beginning of the meal. It then decreased gradually to a nadir of  $-0.41 \pm 0.46$  mmol/l below baseline by 140 min and increased slowly to  $0.40 \pm 0.86$  mmol/l by the end of the experiment (shaded area in Figs. 1 and 2).

In the exercise experiment, the mean postprandial plasma glucose excursion rose slightly but significantly as premeal insulin LP was reduced to 50% ( $2.1 \pm 0.7$  mmol/l;  $n = 18$ ;  $P < 0.05$ ) and to 25% ( $3.6 \pm 0.6$  mmol/l;  $n = 12$ ;  $P < 0.01$ ) of the current dose (LP 100%;  $1.1 \pm 0.56$  mmol/l;  $n = 12$ ). There was a good reproducibility of postprandial glycemic excursion at each premeal insulin LP dose used (CV 31%). An inverse correlation was observed between circulating plasma insulin levels and the postprandial increase in plasma glucose ( $r = -0.49$ ;  $P < 0.001$ ).

During exercise at 25%  $\dot{V}O_{2\max}$  for 60 min, the mean decrease in plasma glucose was not significantly different after LP 50% compared with LP 100% ( $3.25 \pm 0.52$  vs.  $2.95 \pm 0.66$  mmol/l per 60 min). At both insulin doses, more than two-thirds of the glycemic decrease occurred during the first 30 min of the exercise. The glycemic decrease after LP 50% was



**Figure 1**—Changes in plasma glucose before, during, and after exercise at 25% (A) (n = 6) and 50% (B) (n = 6) VO<sub>2max</sub> for 60 min after premeal LP 100% (○), LP 50% (■), and LP 25% (▲). The shaded area represents mean ± SEM postprandial plasma glucose at rest (n = 8). Data are expressed as means ± SEM. \*P < 0.05 by repeated measures using ANOVA.

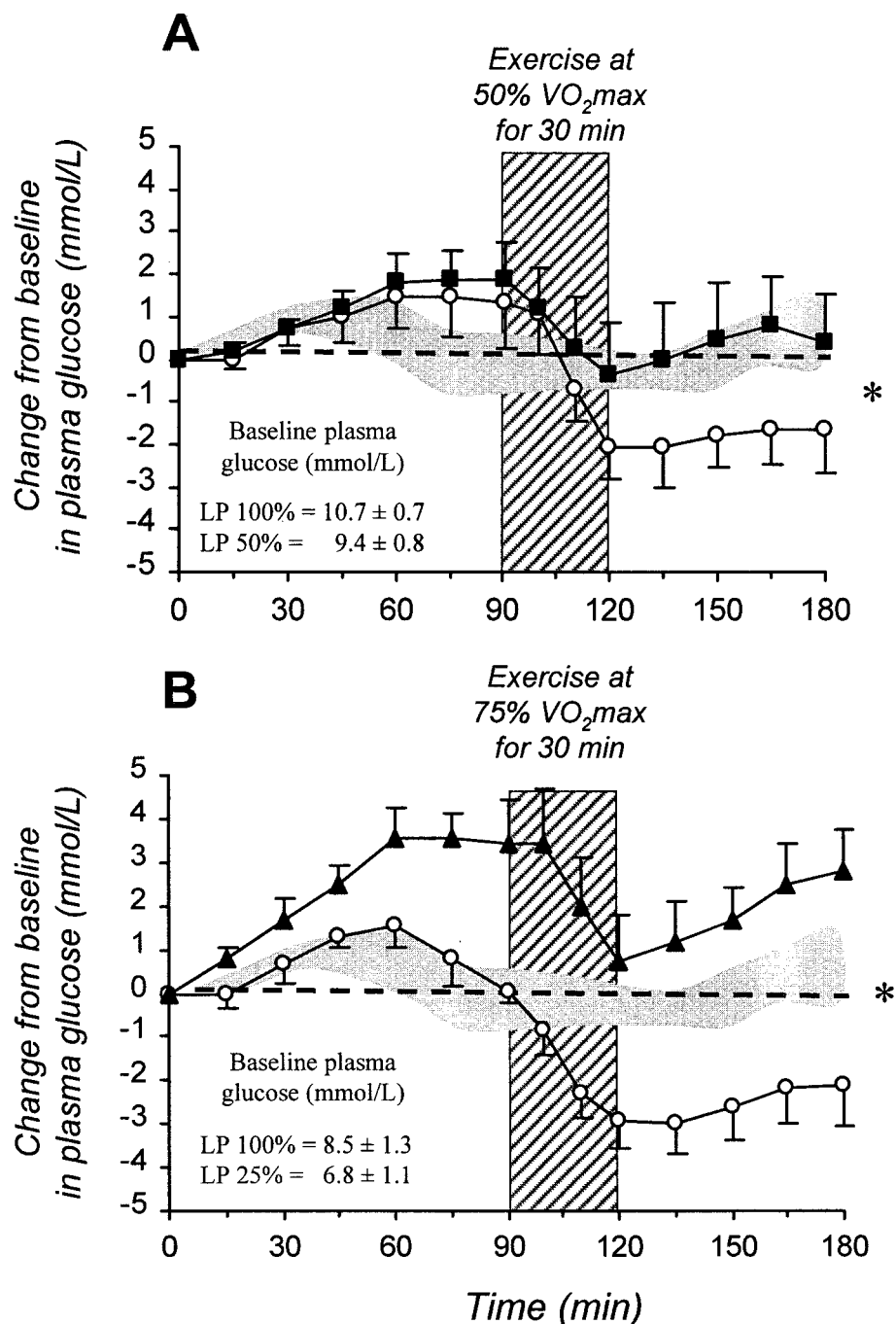
compensated for by the higher plasma glucose level at the beginning of exercise and resulted in a much safer glycemic profile than after LP 100%. Plasma glucose at the end of the exercise was

−2.90 ± 1.13 mmol/l below baseline after LP 100% compared with −0.62 ± 0.93 mmol/l after LP 50% (Fig. 1A). Overall, the glycemic profile after LP 50% was significantly higher than after LP 100% (P <

0.05) but provided a lower risk of hypoglycemia.

During exercise at 50% VO<sub>2max</sub> for 30 min, the mean decrease in plasma glucose was 3.36 ± 0.76 mmol/l per 30 min after LP 100% compared with 2.26 ± 0.54 mmol/l per 30 min after LP 50% (P = 0.08). Plasma glucose was slightly higher at the beginning of the exercise after LP 50%, resulting in a safer glycemic profile than after LP 100%, with plasma glucose concentration of −0.39 ± 1.26 mmol/l below baseline at the end of the exercise period compared with −2.05 ± 0.67 mmol/l (Fig. 2A). Overall, the glycemic profile after LP 50% was significantly different than after LP 100%, with less risk of hypoglycemia (P < 0.05). When the subjects were submitted to exercise at 50% VO<sub>2max</sub> for 60 min, premeal insulin LP at full dose (LP 100%) was associated with a major decrease in plasma glucose, necessitating dextrose 20% infusion in three of four patients, the fourth of whom finished the exercise period at 3.5 mmol/l (data not shown). For that reason, it was then decided not to study any more patients at LP 100% for this protocol. The mean decrease in plasma glucose during exercise after LP 25% was 3.08 ± 0.53 mmol/l per 60 min compared with 4.18 ± 0.57 mmol/l per 60 min after LP 50% (P = NS). The smaller decrease in plasma glucose after LP 25% and the higher plasma glucose level at the beginning of exercise (3.57 ± 0.61 vs. 1.50 ± 0.60 mmol/l; P < 0.05) resulted in a safer glycemic profile (Fig. 1B). Plasma glucose at the end of the exercise was +0.49 ± 0.5 mmol/l above baseline after LP 25% compared with −2.68 ± 0.59 mmol/l below baseline after LP 50% (P < 0.05). The overall glycemic profile was higher (P < 0.05), with a lower risk of hypoglycemia (Fig. 1B).

During exercise at 75% VO<sub>2max</sub> for 30 min, the mean decrease in plasma glucose was 2.7 ± 0.38 mmol/l per 30 min after LP 25% compared with 3.0 ± 0.71 mmol/l per 30 min after LP 100% (NS) (Fig. 2B). However, because plasma glucose was higher at the beginning of exercise after LP 25%, the resulting overall glycemic profile was higher (P < 0.05) with a decreased risk of hypoglycemia. The plasma glucose level at the end of the exercise period was +0.71 ± 1.09 mmol/l above baseline after LP 25% compared with −2.94 ± 0.59 mmol/l below baseline after LP 100% (Fig. 2B; P < 0.05).



**Figure 2**—Changes in plasma glucose level before, during, and after exercise at 50% (A) ( $n = 6$ ) and at 75% (B) ( $n = 6$ )  $VO_{2max}$  for 30 min after premeal LP 100% (○), LP 50% (■) and LP 25% (▲). The shaded area represents mean  $\pm$  SEM postprandial plasma glucose at rest ( $n = 8$ ). Data are expressed as means  $\pm$  SEM. \* $P < 0.05$  by repeated measures using ANOVA.

During the 1-h postexercise recovery period, plasma glucose rose slightly and gradually in an inverse relationship with the premeal insulin LP dose. The increase was  $0.66 \pm 1.4$  mmol/l after LP 100% ( $n = 16$ ),  $0.90 \pm 1.9$  mmol/l after LP 50% ( $n = 12$ ), and  $2.25 \pm 1.1$  mmol/l after LP

25% ( $n = 12$ ) compared with  $0.98 \pm 0.52$  mmol/l in the last 60 min of the resting protocol ( $n = 8$ ) (Figs. 1 and 2). There was an inverse correlation between plasma insulin levels and the postexercise increase in plasma glucose ( $r = -0.51$ ;  $P < 0.001$ ).

Mean free plasma insulin at baseline was  $70.6 \pm 3.6$  pmol/l ( $n = 60$ ); there was no significant difference between the various experimental protocols. After the premeal insulin LP injection, plasma insulin peaked by 60 min at  $188.5 \pm 18.3$  pmol/l after LP 100% ( $n = 22$ ), at  $148.3 \pm 16.0$  pmol/l after LP 50% ( $n = 18$ ), and at  $120.7 \pm 7.25$  pmol/l after LP 25% ( $n = 12$ ). Free plasma insulin levels decreased gradually during exercise; the mean decrease in plasma insulin was related to the duration of exercise ( $15.1 \pm 5.2$  pmol/l after 30 min and  $37.0 \pm 5.6$  pmol/l after 60 min) but was not affected by the exercise itself or by its intensity. In the recovery period, plasma insulin kept decreasing at the higher insulin doses (LP 100% and LP 50%) but not at the lowest dose, suggesting that at LP 25%, basal insulin levels (supplied by UL) had been reached by 120 min.

Mean baseline plasma glucagon, at  $53.4 \pm 4.7$  ng/l ( $n = 60$ ), was similar in all experimental protocols. In response to the standardized breakfast, there was a small but consistent increase in plasma glucagon ( $61.0 \pm 4.7$  ng/l) ( $n = 60$ ), which was totally independent of the absolute premeal insulin LP dose. During the exercise and recovery period, plasma glucagon remained relatively stable until the end of the experiment.

No severe hypoglycemia was observed in any of the experiments. During the 60 experiments performed, 24 episodes of minor hypoglycemia were recorded either during the experiments or in the 18-h postexperiments; two episodes occurred during the resting experiment and 22 episodes occurred during the exercise protocols. Only four hypoglycemic episodes occurred during exercise, each during the 60-min exercise at 50%  $VO_{2max}$  after LP 100%. Decreasing the premeal insulin LP dose to recommended levels reduced the incidence of hypoglycemic episodes by 75%, from 64 to 16 episodes per 100 exercising sessions.

**CONCLUSIONS**— The present study demonstrates that in well-controlled type 1 diabetic subjects on intensive insulin therapy using UL as basal insulin and insulin LP as premeal insulin, glucose homeostasis can be preserved during postprandial exercise of different intensities and different durations by appropriate reduction of premeal insulin LP.

It was decided to study the effects of exercise starting 90 min after the beginning of the meal because it seems to be a convenient time for most subjects participating in planned physical activities for a number of practical reasons. Most people work during the daytime and, therefore, usually plan evening exercise after dinner; also, 90 min is the time it usually takes to get ready and reach a sport facility. Furthermore, exercising on a full stomach is usually associated with discomfort. We chose to study exercise at mild, moderate, and high intensities, so that we were able to advise type 1 diabetic subjects about any type of physical activities they had chosen. Finally, we investigated exercise at durations of 30 and 60 min because they are the most frequent durations (17). It was hoped that the present study, because of these various criteria, would provide information that would apply to most type 1 diabetic patients planning postprandial exercise.

The present investigation clearly shows that postprandial exercise will always be associated with an increased risk of hypoglycemia if the premeal insulin dose is not reduced (Figs. 1 and 2). This seems to be particularly true when using the very fast- and short-acting insulin analog LP, as suggested by Tuominen et al. (18). In our study, more than two-thirds of hypoglycemic episodes occurred with the full premeal insulin dose (Table 1). This is certainly an underestimation, because we had to discontinue the 60-min exercise at 50%  $VO_{2max}$  after LP 100% because four subjects experienced hypoglycemia, three of whom required dextrose 20% infusion. It is worth noting that during exercise of different intensities, the decrease in plasma glucose was close to 3.0 mmol/l during the first 30 min, when the full dose of insulin lispro was used. This is slightly higher than the published data obtained under similar conditions with regular insulin (5,19,20) but comparable to the study performed with insulin LP (18). It should be noted that even at low-intensity exercise (25%  $VO_{2max}$ ), LP 100% was associated with a significant decrease in plasma glucose ( $2.95 \pm 0.66$  mmol/l per 60 min), increasing the risk of hypoglycemia. Therefore, any planned postprandial exercise in well-controlled type 1 diabetic subjects should always be preceded by a reduction in the premeal insulin dose. However, the amount of reduction remains in question.

It was decided a priori that any reduction in premeal insulin LP before exercise would be considered appropriate if it resulted in plasma glucose at the end of exercise similar or close to that measured before the preceding meal. The data show that this was achieved in all the exercise protocols of different intensities and different durations (Figs. 1 and 2). Very few studies have investigated the magnitude of necessary dose reduction to prevent exercise-induced hypoglycemia (17,20–22). Furthermore, this is the first study in which insulin dose reductions are tested at different intensities and different duration in comparable protocols. Schiffrin and Parikh (20) suggested that for a 45-min exercise session at 50%  $VO_{2max}$  90 min after a standard meal, a 30–50% reduction in the premeal insulin (regular) dose was necessary to avoid per-exercise hypoglycemia whether multiple subcutaneous insulin injections or continuous subcutaneous insulin infusions were used. This is consistent with our observations, which we have extended to include exercises of lower and higher intensities and of different durations. The present findings indicate that the proposed dose reductions in the various exercise protocols can be considered appropriate because they resulted in a safer glycemic profile with a decreased risk of hypoglycemia.

The improved glycemic profile during exercise was obtained at the cost of a slightly higher plasma glucose level before exercise as well as during the immediate postexercise period. The higher postprandial plasma glucose at lower insulin LP doses was due to lower circulating plasma insulin. In fact, there was a good inverse correlation between the increase in postprandial plasma glucose and plasma insulin levels. However, the increase in postprandial plasma glucose was relatively small, less than 4 mmol/l, even at LP 25% (Figs. 1B and 2B). This is a minor problem for the decreased risk of exercise-induced hypoglycemia obtained. As for the increase in plasma glucose in the immediate postexercise period, it was only significant at the lowest insulin LP dose (LP 25%) (Figs. 1B and 2B). At LP 25%, circulating plasma insulin in the postexercise period was at or close to basal levels, suggesting that the contribution of insulin LP at that low dose to circulating insulin had nearly disappeared. The lower insulin levels would result in

**Table 1—Guidelines for the reduction of the premeal insulin LP dose in relation to the intensity and duration of postprandial exercise**

Exercise intensity (% $VO_{2max}$ )	% Dose reduction	
	30 min of exercise	60 min of exercise
25	25*	50
50	50	75
75	75	—

\*Extrapolated.

decreased glucose disposal and explain, at least in part, the increase in plasma glucose during the recovery period. Furthermore, the lower insulin-to-glucagon ratio could be associated with an increase in hepatic glucose production, which could also contribute to the elevation of plasma glucose (23). Again, this slight increase in plasma glucose (<4 mmol/l) is a minor price to pay for the decreased risk of hypoglycemia.

Appropriate reduction of the premeal insulin LP dose before exercise resulted in a major diminution of hypoglycemia from 18 to 4 episodes (75% reduction). This decrease is most likely an underestimation, because we only studied four subjects at 50%  $VO_{2max}$  for 60 min after LP 100%, because three of four subjects experienced hypoglycemia. Furthermore, this must be evaluated while taking into consideration that there were also two episodes of minor hypoglycemia in the eight experiments performed on resting subjects; this is consistent with the observed increased incidence of hypoglycemia in type 1 diabetic patients on intensive insulin therapy (24). It is also noteworthy that no hypoglycemic episode occurred during exercise when insulin was reduced appropriately. Therefore, the present study demonstrates that appropriate insulin reduction significantly decreases the risk of hypoglycemia. The data also show that under these conditions, hypoglycemia is very unlikely during exercise. Hypoglycemia in the postexercise period, however, can still occur despite appropriate insulin reduction. It is possible that if the exercise is performed after breakfast or after lunch, insulin before the next meal should also be decreased to avoid any late hypoglycemia (25). If exercise is performed after the evening meal, maybe a larger bedtime

snack should be taken. Further studies are needed to answer these questions.

Nevertheless, the present investigation is sufficiently robust to formulate guidelines for well-controlled type 1 diabetic patients on intensive insulin therapy, using UL as basal insulin and LP as premeal insulin, who would like to participate in planned postprandial exercise (Table 1). It must be understood that these guidelines are considered as a safe starting prescription for patients planning postprandial exercise. Each patient will have to monitor his or her capillary blood glucose very closely before, during, and after exercise and make individual adjustments if necessary. Only then will they be able to decrease the risk of exercise-induced hypoglycemia to a minimum. We believe that such guidelines, if part of an education program, should allow the safe prescription of postprandial exercise in type 1 diabetic subjects.

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