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ABSTRACT

Purpose: To describe a newly developed algorithm, which estimates the glucose supplement on a patient- and situation-specific basis and to test whether these amounts would be appropriate for maintaining blood glucose levels within the recommended range in exercising type 1 diabetic patients.

Methods: The algorithm first estimates the overall amount of glucose oxidized during exercise on the basis of patient's physical fitness, exercise intensity and duration. The amount of supplemental carbohydrates to be consumed before/during the effort represents a fraction of the burned quantity depending on the patient's usual therapy and insulin sensitivity, and on the time of day the exercise is performed. The algorithm was tested in 27 patients by comparing the estimated amounts of supplemental carbohydrates to the actual amounts required to complete 1-hour constant intensity walks. Each patient performed 3 trials, each of which started at different time intervals following insulin injection (eighty-one walks were performed overall). Glycemia was tested every 15 min.

Results: In 70.4% of the walks, independent of the time of day, the amount of carbohydrates estimated by the algorithm would be adequate to allow patients to complete the exercise with a glucose level within the selected thresholds (i.e. 3.9 - 10 $mmol \cdot L^{-1}$).

Conclusions: The algorithm provided a satisfactory estimate of the carbohydrates needed to complete the exercises. Although the performance of the algorithm still require testing for different exercise intensities, durations and modalities, the results indicates its potential usefulness as a tool for preventing immediate exercise-induced glycemic imbalances (i.e. during exercise) in type 1 diabetic patients, in particular for spontaneous physical activities not planned in advance, thus allowing all insulin-dependent patients to safely enjoy the benefits of exercise. **Keywords:** Exercise metabolism; insulin concentration; blood glucose level; Decision Support System, model

INTRODUCTION

Paragraph Number 1 In type 1 diabetic patients (T1DM) exercise improves insulin sensitivity (20, 39) and, together with diet and insulin therapy, may help to achieve and maintain a better metabolic control (1, 36). Regular moderate-intensity physical activity is strongly recommended in these patients (1, 43) because of its protective effects against several cardiovascular risk factors (18, 25, 27). Moreover, exercise can enhance psychological well-being by increasing self-esteem and quality of life (40). The exercise-associated glycemic imbalances, however, remain an unresolved clinical challenge for these patients.

Paragraph Number 2 The mechanism responsible for the exercise-related hypoglycemia in T1DM has generally been attributed to the large exercise-induced rise in muscle glucose uptake not matched by a concomitant increase in hepatic glucose production (40). A blunted counter-regulatory response may exacerbate this mismatch (10, 14). To counter the risk of an excessive fall of blood glucose, various reductions in the pre-meal insulin dose have been proposed (29, 34), which, however, require the exercise to be planned and often does not exempt patients from a carbohydrate supplement (15). Moreover, in many instances exercise is unexpected and the insulin dose cannot be modified ahead of time; hence additional glucose ingestion is the only measure to attenuate the exercise-induced lowering of glycemia (24, 35).

Paragraph Number 3 Existing guidelines for minimizing the risk of an excessive fall of blood glucose level (1, 8, 9, 23, 24, 40) are still vague, and thus-each patient has to discover, by trial and error, his/her own strategy. Several attempts are usually required to gain sufficient experience so that fear of hypoglycemia is still the strongest barrier to physical activity, while the number of difficulties to meet with often further discourage patients (5).

Paragraph Number 4 It is well known that exercise intensity and duration, the prevailing insulin level (i.e. the time of day exercise is performed), and the level of glycemia before

exercise influence the amount of carbohydrate supplement (24). These parameters, however, are scarcely accounted for in the existing guidelines, while the influence of physical fitness and insulin sensitivity are even less examined (24).

Paragraph Number 5 Recent work by our group has revealed a linear relationship between actual blood insulin concentration and the glucose supplement needed to prevent hypoglycemia during moderate exercise (12), even when expressed as percentage of the overall glucose burned during the effort. In turn, the overall glucose oxidation rate during aerobic exercise, i.e. below the anaerobic threshold, increases with increasing heart rate (HR) and can thus be easily estimated (11). Accordingly, we hypothesized that it would be possible to estimate, on a patient- and situation-specific basis, the amount of supplemental carbohydrates required by T1DM patients before/during aerobic exercise to achieve end-exercise blood glucose levels between the hypoglycemic threshold of 3.9 $mmol \cdot L^{-1}$ (13) and the maximal random glucose target of 10 $mmol \cdot L^{-1}$ (2). Consequently, we developed a new algorithm (called ECRES, Exercise Carbohydrate Requirement Estimating Software), whose main peculiarities are: 1) it is based on the patient's habitual therapy and diet and no changes in the insulin dose are usually mandatory; 2) patient's insulin sensitivity is taken into account through the individual dietary carbohydrate-to-insulin ratio; 3) actual exercise intensity and duration are used for the estimate; 4) patient's physical fitness is considered when the overall amount of glucose oxidized is estimated, and 5) the carbohydrate supplement can be calculated for any time of day the exercise is performed.

Paragraph Number 6 First objective of this paper is to describe the developed algorithm. Second aim is to verify whether the amounts of carbohydrates estimated by the algorithm do not differ significantly from the actual required amounts. To this aim, T1DM patients performed, in different days, three 1-hour moderate intensity walks starting at three different time intervals following the midday insulin and the amounts of administered supplemental

carbohydrates were compared to those estimated by the ECRES algorithm.

METHODS

The ECRES algorithm

Paragraph Number 7 A formally setting procedure has to be run at first (Figure 1, panel A), which deals with the patient's specific data. The daily profile of total insulin concentration at time *t*, *totIC(t)*, is estimated first, based on the patient's usual therapy data (insulin *i*) and on "standard" pharmacokinetic profiles of the insulin analogues, *IT(i,t),* loaded in the system (21, 22, 31). The *IT(i,t)* are realigned to the scheduled times of injection, $\tau(i)$, and scaled proportionally according to the ratio between the patient's dose, *PID(i)*, and the standard dose, *SID(i)*, for the specific insulin:

$$IC(i,t) = IT(i,t-\tau(i)) \cdot \frac{PID(i)}{SID(i)}, \quad (1)$$

$$totIC(t) = \sum_{i=1}^{n} IC(i,t). \quad (2)$$

with *n* being the number of different insulin types.

Paragraph Number 8 Subsequently, the overall amount of insulin, *totIU(j),* acting between one injection and the following (with the exception of evening, for which 6 hours are considered after the supper time insulin injection) is calculated as:

$$totIU(j) = \sum_{t \in jth\text{-}period} totIC(t), \quad (3)$$

and the amount of dietary carbohydrates assumed during the *j*th time period, *totCHO(j)*, is computed. These data allow us to calculate the patient's carbohydrates-to-insulin ratios for three time intervals (*j*=morning, afternoon and evening), as shown below, in order to account for differences in insulin sensitivity among patients and throughout the day.

Paragraph Number 9 The total daily insulin profile is thus converted to a daily insulin profile that we define as "efficacious", applying the patient's specific carbohydrates-to-insulin ratios for each *j*th time period, *effIC(t,j)*:

$$effIC(t,j) = totIC(t) \cdot \frac{totCHO(j) \,/\, totIU(j)}{k} \quad (4)$$

where *t* is within the *j*th period and *k* is the average carbohydrates-to-insulin ratio observed in our previous work (i.e. 4.836 g/IU) (12). The time profile of the carbohydrate percentage needed to maintain glucose level within the recommended range during exercise, *%CHO(t,j)*, is then obtained by applying, for each time point of the *effIC(t,j)* profile, the linear relationship between the percentage of carbohydrates and insulin concentration illustrated in our previous work (12):

$$\%CHO(t,j) = effIC(t,j) \cdot 4.3983 + 10.7642 \quad (5)$$

Paragraph Number 10 Finally, the glucose oxidation rates per minute exercise, *oxCHO(hr)*, are computed for all the heart rates, *HR(i)*, ranging from rest to maximal heart rate for aerobic exercise, in turn calculated as 70% of age-predicted maximum heart rate (i.e. 220 – age):

$$oxCHO(hr) = m \cdot HR(i) + q \quad (6)$$

where the *m* and *q* values are those reported in a previous work by our group (11) for trained and untrained patients.

Paragraph Number 11 The second procedure (Figure 1, panel B) runs on each exercise occasion and deals with the actual characteristics of the effort (i.e. intensity, duration, starting time of day) and the actual metabolic conditions (i.e. glucose level). According to expected exercise intensity (defined by HR = *ehr*) and duration, *eD*, an estimate of the total amount of glucose oxidized during the effort, *totCHO*, is calculated as:

$$totCHO = oxCHO(ehr) \cdot eD \quad (7)$$

Subsequently, the theoretically amount of supplemental glucose, *reqCHO,* is calculated by selecting the appropriate percentage of *reqCHO* needed to prevent hypoglycemia, *%CHO(t,j)*, according to the time of day the exercise is performed and the time elapsed from the last insulin injection:

$$reqCHO = totCHO \cdot \frac{\%CHO(t, j)}{100}. \quad (8)$$

Paragraph Number 12 Whenever exercise is planned in advance, the administration of a reduced insulin dose may be warranted to hold down the carbohydrate supplement. To satisfy this condition, the software is able, optionally and for the specific exercise occasion, to estimate the carbohydrate supplement according to the varied insulin dose while patient's usual carbohydrates-to-insulin ratio is kept constant.

Paragraph Number 13 The excess/lack of glucose, *CHOE*, contained in the extra-cellular fluid compartment is then computed as the product between the extra cellular fluid volume, *ECF*, and the difference between actual glycemia (*aGL)* and the theoretical glycemia the subject should have at the time of exercise, *theoGL(t),* i.e. the target glucose level recommended for T1DM patients at the same time distance after a meal (7, 38):

$$CHOE = (aGL - theoGL(t)) \cdot ECF. \quad (9)$$

In turn, to take into account also for a gender difference, *ECF* is estimated as 0.27 $L \cdot kg^{-1}$ in men and 0.225 $L \cdot kg^{-1}$ in women (26), values not far from the glucose distribution volume reported by the literature (32). Thus, the actual amount of carbohydrates needed to prevent glycemic imbalances during exercise, *actCHO*, is calculated by:

$$actCHO = reqCHO - CHOE. \quad (10)$$

Paragraph Number 14 The *actCHO* can be fully consumed before or during the exercise. Finally, a rough estimate of the additional carbohydrates needed to prevent late-onset glycemic imbalances (*lateCHO*) is calculated as the difference between the overall amount of

glucose oxidized during the exercise and the amount of CHO required to maintain glycemia near the normal level during the effort:

$$lateCHO = totCHO - reqCHO. \quad (11)$$

The consumption of the *lateCHO* has to be distributed over the 24 hours after the exercise. Unfortunately, no clear-cut guidelines are at the moment available to patients suggesting how to best arrange this extra amount of carbohydrates; we plan to investigate this problem in the near future.

The described algorithm was implemented in a software, which allows to print a tabular output summarizing, for each patient, the glucose oxidation rate (*oxCHO(hr)*) for heart rates ranging from rest to maximal aerobic exercise, the percentage of required carbohydrates as a function of the time distance from the last insulin injection *(%CHO(t,j)*) for the morning, afternoon and evening periods, and the excess/lack of glucose solved in the body (*CHOE*) on the basis of glycemia. At each exercise occasion outside the laboratory, patients were instructed how to estimate their carbohydrates requirement using the data of the table and making few simple calculations, according to the second procedure described above.

Study population

Paragraph Number 15 Twenty-seven T1DM patients (19 men, 8 women; average HbA_{1c} 7.2 ± 1.1%) aged 44 ± 11 years, diagnosed with type 1 diabetes 22 ± 11 years before recruitment, participated in the study after having been informed of its nature, purpose, and possible risks. All patients signed a written informed consent. On average, patients weighted 72 ± 11 kg and were 1.74 ± 0.09 m tall (BMI 24 ± 2 $kg \cdot m^{-2}$); mean daily insulin dose was 0.56 ± 0.12 $IU \cdot kg^{-1} \cdot day^{-1}$. Patients were not affected by other chronic diseases, and had no evidence of diabetes complications contraindicating physical activity. All patients were on a basal-bolus insulin regimen; nineteen patients used lispro insulin before meals, seven used regular insulin

and one used the Mix50 formulation; twenty one patients used insulin glargine at bed time, while the other six used insulin NPH. The study was approved by the local Ethical Committee and was conducted according to the Declaration of Helsinki.

Paragraph Number 16 To mimic an outpatients setting, volunteers were classified according to the self-reported physical activity habits as "aerobically trained" (12M, 7F), who exercised regularly at least 30 minutes for 3 days/week, and "sedentary" (7M, 1F), who exercised only occasionally. In addition, the common equation 220 – age was used to estimate the age-predicted maximum theoretical heart rate.

Experimental protocol

Paragraph Number 17 Patients were advised to maintain their usual diet and insulin regimen, to control their blood glucose levels according to the self-management procedures in order to avoid the occurrence of hypoglycemic events, and to refrain from unusual physical activities 24 h prior to the walks.

Paragraph Number 18 In an outpatient setting, each volunteer repeated three times, in random order and at least three days apart, a constant intensity aerobic treadmill walk of one hour duration (thus, in total were performed eighty-one walks) starting at different time intervals (90 min, 180 min, and 270 min) following the lunch (midday) insulin treatment (i.e. the walks started at 2:30 PM, 4:00 PM and 5:30 PM, respectively). Patients were instructed to have lunch at 1.00 PM before all the three walks and to give the injection in the abdominal area. Habitual insulin dose and diet were followed before the walks, with the exception of the trial starting 90 min after lunch. Before these walks, in order to restrain the carbohydrate supplement, patients were instructed to half the usual insulin dose and the amount of carbohydrates of the midday meal. The usual premeal insulin dose amounted to 9.9 ± 4.0 U and the average carbohydrate intake amounted to 102 ± 31 g. Before each trial the same

endocrinologist checked verbally the actual applied insulin dose and the amount of ingested carbohydrates and directly supervised each exercise session.

Paragraph Number 19 The treadmill used (Saturn, H-P Cosmos, Traunstein, Germany) automatically adjusted speed and/or slope so that the target HR (i.e. 65% of individual maximal theoretical HR) was held constant.

Paragraph Number 20 All the patients arrived at the laboratory about 45 min prior to the start of the scheduled walk and were immediately equipped with the belt of the HR monitoring system (Polar Electro, Kempele, Finland) to acquire HR every 15 s throughout exercise; HR data were subsequently averaged over 15 min periods. Half an hour before the start of exercise, ketone bodies and glycemia were determined by means of appropriate reactive strips (MediSense Optium β-chetone, Abbott Laboratories, Australia, and Accu-Check™ Active, Roche Diagnostics, Switzerland, respectively). Thereafter, patients were administered (in the form of sugar or sugar-drops) approximately 70% of the amount of carbohydrates estimated by the ECRES algorithm to counter hypoglycemia during exercise (i.e. *actCHO)*, calculated as difference between the fraction of the glucose burned (depending on insulin concentration and sensitivity) and the excess glucose already solved in the body. Glycemia was determined again at the start of exercise and then every 15 minutes (or more frequently, if necessary) until the end of the exercise. The remaining fraction (30%) of the estimated carbohydrate requirement was administered in two further equal amounts at 15 min and 30 min of exercise only if glycemia was within the recommended range. In the case glycemia fell below 5.0 $mmol \cdot L^{-1}$ (13) patients were given additional known amounts of sugar (5 g each time).

Paragraph Number 21 Unfortunately, no clear-cut guidelines are at the moment available suggesting patients how to face the risk of late-onset hypoglycemia. So, after the exercise sessions, all our patients were suggested to consume the amounts of carbohydrates corresponding to the *lateCHO* estimated by the algorithm, calculated as difference between

the overall amount of glucose burned (which depends on exercise intensity and was essentially the same in the three trials) and the amount of glucose required to prevent hypoglycemia during the exercise (which increases with increasing insulin concentration). Accordingly, the amount of carbohydrates required to avoid late-onset hypoglycemia were estimated to amount on average to 9 ± 17 g, 13 ± 20 g and 34 ± 24 g for the three trials, respectively. On the basis of our previous clinical experience, the overall post-exercise carbohydrate supplement was distributed, in the form of starch, as follows: 20% between the end of exercise and supper, 40% added to the evening meal, 25% added to breakfast in the following morning and the remaining 15% at lunch. In addition, patients were instructed to check their glucose level every hour from end-exercise until bed-time and every two hours during the following morning. Sedentary patients were also suggested to reduce by about 10% their subsequent rapid-acting insulin dose and by 5% the long-acting insulin dose. An endocrinologist from our group remained on call by phone at any time during the 24-hours following the trials to help patients in facing possible glycemic imbalances. Patients were asked to record all the glycemic levels on appropriate forms, the analysis of which confirmed us that the occurrence of late-onset hypoglycemia after the trials was actually avoided in all cases.

Data analyses

Paragraph Number 22 Despite the instructions given to the patients, a HYPO group could be made up by collecting the trials performed after a hypoglycemic event occurred during the 24 hours preceding the walks (n=42), the remaining cases constituting an EU group (n=39).

The comparison of the amounts of carbohydrates estimated by the ECRES algorithm with the actually administered ones allowed us to assign the walks to three groups (identified by a categorical value). The grouping criteria were: 1) the amount of carbohydrates estimated by

the ECRES algorithm was insufficient, thus additional amounts of sugar had to be administered (INS group); 2) the amount of carbohydrates estimated by the algorithm was excessive and was not completely administered (EXC group); 3) the amount of carbohydrates estimated by the algorithm was adequate to allow patients complete the exercise with the glucose level between the hypoglycemic threshold of 3.9 $mmol \cdot L^{-1}$ (13) and the maximal random glucose target of 10 $mmol \cdot L^{-1}$ (2) (AD group).

Paragraph Number 23 Data were treated according to standard statistical procedures using Systat vs. 11 software. For continuous variables, analysis of variance was applied to investigate differences among the walks scheduled at different times of the day, while repeated measures testing was used when measurements were repeated within a group. Bonferroni post-hoc and difference contrast were applied when appropriate. Kruskal-Wallis analysis of variance was used to test for significant differences among groups of categorical values. Linear correlation was assessed by the least-square method. Bland and Altman's limits-of-agreement plot (3) was employed to assess the level of agreement between the actually administered carbohydrates and the estimated ones. A value of $P < 0.05$ was considered statistically significant.

Paragraph Number 24 Preliminary testing showed no statistical differences between the trained group of individuals and the sedentary subjects; the two groups matched for either the anthropometric and clinical characteristics of the volunteers (unpaired t-test; P = NS) and the main outcome of the study, i.e. the percentage trials for which the estimated amount of carbohydrates would have been adequate, insufficient or excessive (Kruskal-Wallis test; P = NS). The data of the two groups (trained and untrained subjects) were thus pooled and are illustrated together.

Paragraph Number 25 Similarly, preliminary testing showed that only glycemia half an hour before the start and at the end of the exercise was significantly lower in the HYPO group as

compared to the EU group (7.4 ± 2.6 vs. 10.3 ± 3.5 mmol·L^{-1} and 6.3 ± 2.6 vs. 8.2 ± 3.0 mmol·L^{-1}, respectively; unpaired t-test, n = 81, $P < 0.005$ for both). However, since the fall of glycemia during exercise and the amount of supplemental carbohydrates were not significantly different between the two groups (unpaired t-test, n = 81, P = NS for both), and the percentage trials assigned to the INS, EXC and AD groups did not differ (Kuskal-Wallis test, P = NS), the two groups (HYPO and EU) were pooled and are illustrated together.

RESULTS

Paragraph Number 26 None of the patients had measurable ketone bodies before any of the walks.

Average HR during the exercises was 114 ± 7 bpm; HR reached the target value in a few minutes, and thereafter remained stable over time (MANOVA, Time effect, P = NS), without any difference among the three trials (MANOVA, Trial effect, P = NS).

Average glucose level half an hour before the start of the exercises amounted to 8.9 ± 3.4 mmol·L^{-1}; it increased to 9.6 ± 3.3 mmol·L^{-1} at the start of exercise (MANOVA, Time effect, difference contrast, $P < 0.001$) because of the administered carbohydrates and fell significantly to 7.3 ± 3.0 mmol·L^{-1} (MANOVA, Time effect, difference contrast, $P < 0.01$) at the end of the exercises. No significant difference (MANOVA, Trial effect, P = NS) was observed among the three trials. Figure 2 illustrates the individual glucose evolutions of all the walks, from -30 min to the end of the exercises (trials of the same patient being classified in the same group for at least two out of three walks are drawn with individual symbols/lines); values are aligned to the specific start time of the trials and grouped according to the final evaluation of the walk (INS, AD or EXC groups). Average, minimum and maximum glucose levels for the different groups are summarized in Table I.

Paragraph Number 27 Actual administered carbohydrates were independent of the starting

glycemia (Figure 3), while they were significantly different for the exercises scheduled at the three different times of the day (ANOVA, Trial effect, $P < 0.001$), amounting on average to 63 ± 28 g, 44 ± 35 g and 24 ± 23 g, respectively. The estimated amounts of supplemental carbohydrates (estCHO, g) were not significantly different from the actual administered ones (actCHO, g; paired t-test, P = NS, n = 81). The two quantities were linearly related to each other as illustrated in Figure 4, panel A. Independent of the different time scheduling of the walks, the relationship is described by:

$$\text{actCHO} = 0.96\ \text{estCHO} + 1.74 \qquad (n = 81,\ R^2 = 0.870,\ P < 0.001)$$

The Bland–Altman plot between actCHO and estCHO (Figure 4, panel B) shows: 1) no trend in the data as the mean carbohydrate supplement increases, 2) a 95% confidence interval ranging from -24.3 to +24.5 g, and 3) a bias of 0.1 g.

Paragraph Number 28 Altogether, 11 walks out of 81 (13.6%) were assigned to the INS group (open dots in Figures 3 and 4); the underestimation of estCHO in this group amounted on average to 18.1 ± 11.8 g (0 - 46.3 g). At the other extreme, 13 cases (16.0%, open squares in Figures 3 and 4) were assigned to the EXC group, their overestimation in the supplemental carbohydrates amounting to 10.1 ± 19.8 g (0 - 63.7 g). The remaining 57 walks (70.4%, full dots in Figures 3 and 4) were assigned to the AD group, i.e. in these trials the amount of carbohydrates estimated by the algorithm was adequate to allow patients ending the exercise with the glucose level within the selected thresholds; in this group the difference with actCHO amounted on average to -1.2 ± 3.7 g (-11.9 - 5.8 g). Average glucose level at the end of the walks in the AD group amounted to 6.7 ± 1.6 mM (3.9 - 9.7 mM). The difference to the hypoglycemic and the hyperglycemic thresholds amounted to 2.8 ± 1.6 mM (0 - 5.8 mM) and to 3.3 ± 1.6 mM (0.3 - 6.1 mM), respectively, corresponding to a grand average difference in

the supplemental carbohydrates of -0.8 ± 11.9 g (-24.9 - 25.4 g). The percentages of walks assigned to INS, EXC and AD groups were not significantly different among the three times of day the exercises were performed (Kruskal-Wallis test, *P* = NS) (Figure 5).

DISCUSSION

Paragraph Number 29 The frequent metabolic imbalances experienced by T1DM patients during exercise discourage patients from regular physical activities (5).

Paragraph Number 30 So far no clear-cut guidelines have been proposed to help patients maintain a near physiological glycemia for activities performed at any time of day and under a rather wide range of intensities. Only general strategies have been suggested (1, 23, 24, 29, 33, 34, 40), which, however, require an adequate understanding of the metabolic and hormonal responses to exercise and an individualized trial-and-error approach to adjust time scheduling of exercise, insulin dosage, and/or extra amount of carbohydrates. These vague guidelines may be the consequence of the contrasting effects that different exercises exert on blood glucose level. In fact, patients engaged in high-intensity exercises may experience a progressive rise in blood glucose level (28, 37), while moderate continuous aerobic activities mainly result in a decline of glycemia (8, 12, 35, 42). Without consuming a glucose supplement prior to the effort, about 78% of patients performing moderate-intensity exercise required dextrose infusion to avoid hypoglycemia (8) and blood glucose levels fell below 4.0 $mmol \cdot L^{-1}$ in 45% of physical activities performed by a group of adolescents (35). To oppose the exercise-mediated fall in glucose level, the performance of a single bout or intermittent high-intensity exercise has been proposed (6, 16, 17), because of its effect on the counterregulatory hormones and on the hepatic gluconeogenesis (30). High-intensity exercise, however, may not be appropriate for sedentary, overweight or older individuals, for which a more constant exercise in the aerobic range, in particular walking, is strongly recommended

(4, 19).

Paragraph Number 31 A major limitation of most of the above mentioned studies is that the observations were carried out only at one time interval following insulin administration. The blood glucose responses, however, can be quite different for the same exercise performed at different postprandial times. The greater exercise-induced fall of glycemia during early exercise (42) is in agreement with the notion that the amount of supplemental carbohydrates is greater when exercise is performed at shorter time intervals following insulin administration. Only a tendency for a greater blood glucose response was observed during early postprandial morning exercise as compared to late exercise in patients using intermediate insulin at breakfast, whose effect was probably negligible during early exercise but not more so during late exercise (9).

Paragraph Number 32 The algorithm illustrated in the present paper has been designed to become a tool for helping type 1 insulin-dependent patients to determine, on a patient- and situation-specific basis, the amount of carbohydrates needed before and/or during moderate aerobic exercise (i.e., in the range 55 to 70% of maximal heart rate) to minimize the risk of immediate exercise-induced glycemic imbalance (i.e. during exercise). In fact, several variables influencing glucose metabolism during the effort (e.g. actual exercise intensity and duration, starting time of day, and actual glucose levels) are main parameters for the estimate. The algorithm can be of particular interest when exercise is spontaneous and not planned in advance, and consequently when only the ingestion of extra carbohydrates can prevent hypoglycemia (15, 24, 35). In spite of the rather large amounts of carbohydrates to be ingested in some cases (in particular in sedentary patients), in most of them the overall energy spent will be higher than the amount of energy introduced with the supplement. Moreover, if glycemic imbalances (either hypo- or hyperglycemia) are avoided, exercise will give benefits also on long-term glycemic control. Regularly exercising patients may also take advantage of

the algorithm to face glycemic imbalances during exercise occasions outside their usual training hours; in fact, their higher insulin sensitivity is reflected in the rather low insulin doses, which are main parameters to calculate the supplement.

Paragraph Number 33 The preliminary evaluation of the ECRES algorithm is promising. Independent of the time distance from the insulin injection and without requiring any time-consuming trial-and-error approach, the estimated carbohydrate requirement would be adequate to prevent immediate exercise-induced glycemic imbalances in 70% of the walks. This percentage is not far from the rates obtained for standardized exercises by other authors (41), who, however, do not provide any clear-cut suggestion for exercises scheduled at different times of the day, i.e. when the prevailing insulin concentration may be quite different. The over- and underestimation of the carbohydrate supplement estimated by the algorithm may seem rather high, ranging from -24.3 to +24.5 g. However, when the analysis is restricted to the AD group, the over/underestimation decreases to 1.2 ± 3.7 g, amount that is within a clinically acceptable range.

A limitation of the present study is that only sugar/sugar drops were administered to patients. It can be expected that different types of carbohydrates (e.g. starches) or the contemporary consumption of other nutrients (e.g., fats or proteins), would likely result in a different glycemic response mainly because of a slower glucose absorption from the gut. Under these conditions, the risk of hypoglycemia would continue until glucose is not fully absorbed, while glycemia at the end of exercise might increase.

Major causes of error in the estimation of the supplemental carbohydrates

Paragraph Number 35 The correct assignment of the patient as “sedentary” or “trained” is one of the major sources of error in the estimation of the carbohydrate supplement. As a matter of fact, the overall amount of glucose oxidized during exercise by a sedentary patient

may be twice the quantity of a trained subject (11). Accordingly, the carbohydrate supplement estimated by the ECRES algorithm will also be double. This was the case of one of our patients who was erroneously classified as "trained" while in actuality he was a "sedentary" person. This patient performed three out of the eleven walks for which the estimated amount of carbohydrates would be insufficient (open dots in Figure 2, panel INS). In addition, altough the equations reported in the previous work by our group (11) allow to estimate the glucose oxidation rate in "sedentary" and "active" people, some patients are even more trained than expected. This was likely the case for another patient of ours (open squares in Figure 2, panel EXC): his glucose oxidation rate was lower than that calculated by ECRES and, consequently, the estimated glucose supplement was too high. It has to be pointed out here, however, that the error in the estimate of the overall amount of glucose burned during the effort can be negligible when the exercise is carried out at low intensity (i.e. the overall amount of glucose burned is low), in particular when the activity is performed at least 3-4 hrs following insulin administration (thus when insulin concentration is low and the corresponding fraction of the burned glucose required to maintain euglycemia is also low). On the contrary, for early exercise, the erroneous assignment of patient as "sedentary" or "trained" may be crucial. Undoubtedly, a more precise classification of patients' fitness level would enhance the performance of the algorithm and make less important the related possible error.

Paragraph Number 36 The second major cause of error is patient's insulin sensitivity. This last is assumed to be described by the ratio between the amount of dietary carbohydrates and patient's usual insulin dose. Small changes in the amount of carbohydrates habitually consumed with diet can determine important variations in the calculated ratio, which will significantly affect also the estimate of the supplemental carbohydrates needed for exercise. In our experience, patient's insulin sensitivity is actually represented by the carbohydrates-to-

insulin ratio only if 1-h postprandial glucose level is about 1.7-2.8 mmol · L^{-1} higher than the preprandial level (38).

Paragraph Number 37 Finally, despite a rather regular life style, patients often experience unexplainable hypoglycemic or hyperglycemic events, which are mainly due to unexpected and unpredictable phenomena temporarily affecting patient's insulin sensitivity. In the present investigation, five walks were performed by patients who experienced a hypoglycemic event in the 3-4 hours just preceding the exercise. A transiently enhanced insulin sensitivity may explain either the hypoglycemic events and the greater amount of supplemental carbohydrates required for these trials as compared to the quantities estimated by the ECRES algorithm. At the other extreme, six walks were performed by patients who started the exercise with a very high glucose level (> 13.5 mmol · L^{-1}) lasting since a few hours. A transitory decrease in insulin sensitivity may explain why, under these conditions, the estimated carbohydrate requirement was too high.

Undoubtedly, when calculating the amount of supplemental carbohydrates patients may get wrong in estimating exercise intensity and duration. These errors affect the overall amount of glucose burned during the effort. However, similarly to the erroneous assignment of patient as trained or sedentary, the difference may be negligible when the exercise is carried out at low intensity, in particular when the activity is performed at least 3-4 hrs following insulin administration. On the contrary, for early exercise, the difference may be of greater importance. It can be calculated that, in the worst case (i.e. for a sedentary patient), for a 5 beat per minute error in the estimated intensity, the estimated amount of burned glucose differs of 0.002 g per minute per kg body mass, corresponding to about 8.4 g for a patient of 70 kg who exercises for one hour. To avoid an excessive fall of glycemia, however, only a fraction of the overall amount of glucose burned is required, depending on the time scheduling of the exercise. In addition, after a few minutes of activity, patients can verify

actual heart rate and recalculate the correct requirement, while a further amount of carbohydrates can be estimated to continue exercising when the previous supposed duration is exceeded.

Paragraph Number 38 It can thus be expected that, when the major causes of error discussed above are avoided or appropriately taken into account, the amount of supplemental carbohydrates estimated by the ECRES algorithm will be adequate for an even higher percentage of exercises (e.g. up to 57 out of 64 walks = 89%).

Conclusions

Paragraph Number 39 The algorithm described in the present paper seems adequate for estimating the supplemental carbohydrates required by a T1DM patient to avoid immediate exercise-induced glycemic imbalances (i.e. during exercise) in a high percentage of aerobic exercises, independent of the time of day the activity is performed. Results of the present investigation show that in spite of high pre-exercise glucose levels that may seem high enough to avoid hypoglycemia to develop, in some instances patients need anyhow a carbohydrate supplement. Although the amount of the supplement is estimated on a patient- and situation-specific basis, the algorithm represents only a Decision Support System that can dramatically reduce the time spent for the trial-and-error approach. Nevertheless, since unpredictable factors may influence patient's usual insulin sensitivity and thus the glycemic balance, the use of the algorithm does not exempt patients from controlling their glucose level according to the usual procedures

Paragraph Number 40 Undoubtedly, the performance of the algorithm has been tested only for a moderate intensity walking exercise. In order to safely apply the algorithm on a wide proportion of the diabetic population, its performance has to be tested also for different exercise intensities, durations and modalities. In addition, a comparison with a control group

applying one of the empirical compensations usually taught to patients is needed.

Paragraph Number 41 Unfortunately, no clear-cut suggestions are at the moment available suggesting patients how to best arrange extra amounts of carbohydrates and/or changes in the insulin doses after an exercise session. As a consequence, even the algorithm illustrated in the present paper does not help patients to counter late-onset glycemic imbalances. We plan to investigate this problem in the near future and, subsequently, to enhance the features of the algorithm.

Paragraph Number 42 In conclusion, we believe that the illustrated algorithm can help patients to safely enjoy the benefits of physical activity, in particular if it is spontaneous and not planned in advance. It may be a useful tool for patients whose fear of hypoglycemia is particularly strong, probably because of their difficulties in understanding the metabolic and hormonal responses to exercise, leading to great difficulties in assessing their own strategy.

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FIGURE LEGENDS

Figure 1

Panel A. The daily profile of the percentage carbohydrates needed to prevent hypoglycemia during exercise is estimated based on the patient's individual therapy (i.e. insulin types, doses, time scheduling and dietary carbohydrates).

Panel B. The actual amount of carbohydrates the patient has to consume before/during exercise is estimated based on the exercise specific data (i.e. intensity and duration and starting time of day) and on the glucose level at the start of the activity.

Figure 2

Individual glucose evolutions of all the walks are illustrated from -30 min to the end of the exercises; values are aligned to the specific start time of the trials and grouped according to the final evaluation of the walk (panels INS, AD or EXC). Trials of the same patient being classified in the same group for at least two out of three walks are drawn with individual symbols/lines.

AD: walks concluded with glycemia within the selected thresholds.

INS: walks requiring the administration of additional amounts of carbohydrates.

EXC: walks concluded with a too high glycemia (>10 $mmol \cdot L^{-1}$).

Figure 3

Actual delivered supplemental carbohydrates (g) are plotted as a function of starting glycemia (mM).

Full dots: walks concluded with glycemia within the selected thresholds (i.e. 3.9 - 10 $mmol \cdot L^{-1}$).

Open dots: walks requiring the administration of additional amounts of carbohydrates.

Open squares: walks concluded with a too high glycemia (>10 mmol·L^{-1}).

Figure 4

Panel A: Estimated amounts of carbohydrates (estCHO, g) are plotted as a function of the actual administered amounts (actCHO, g). Overall, the relationship is described by: actCHO = 0.96 estCHO + 1.74 (n = 81, R^2 = 0.870, p < 0.001).

Panel B: Bland-Altman plot between actCHO and estCHO.

Full dots: walks concluded with glycemia within the selected thresholds (i.e. 3.9 - 10 mmol·L^{-1}).

Open dots: walks requiring the administration of additional amounts of carbohydrates.

Open squares: walks concluded with a too high glycemia (>10 mmol·L^{-1}).

Figure 5

Percentage walks are illustrated for the three time schedulings of the exercises.

Open slice: walks concluded with glycemia within the selected thresholds.

Full slice: walks requiring the administration of additional amounts of carbohydrates.

Hatched slice: walks concluded with a too high glycemia (>10 mmol·L^{-1}).

Figure 1

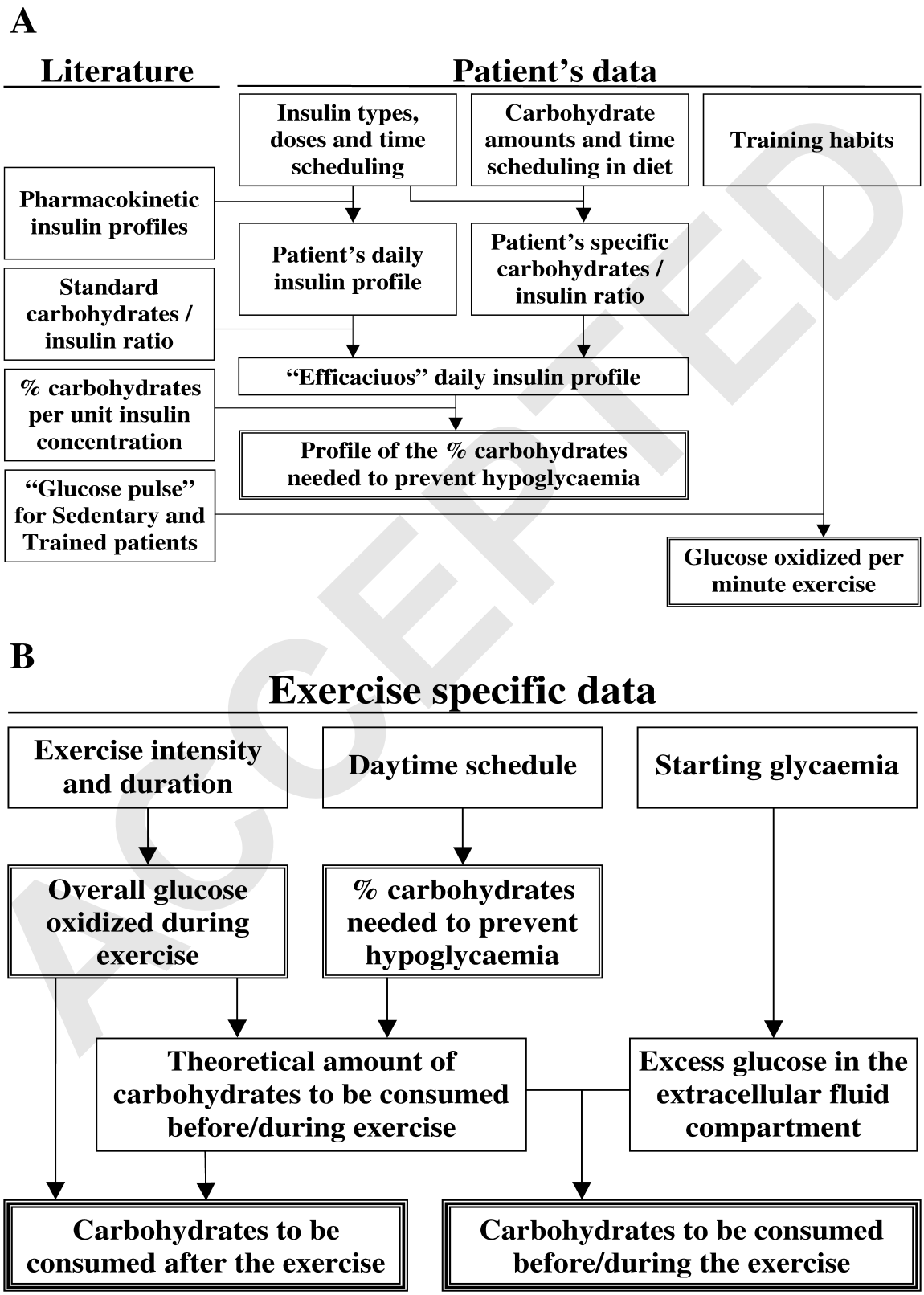

Figure 2

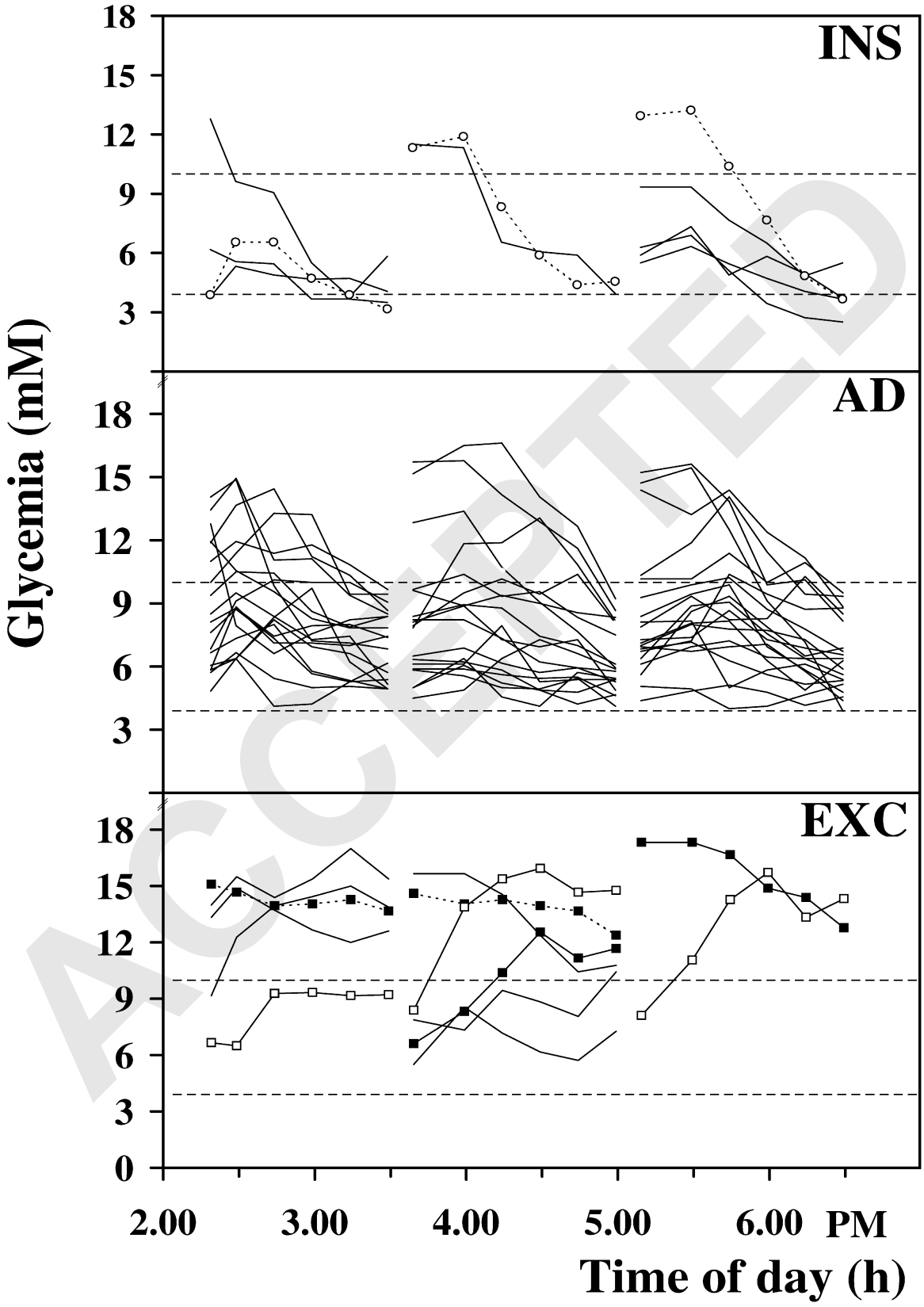

Figure 3

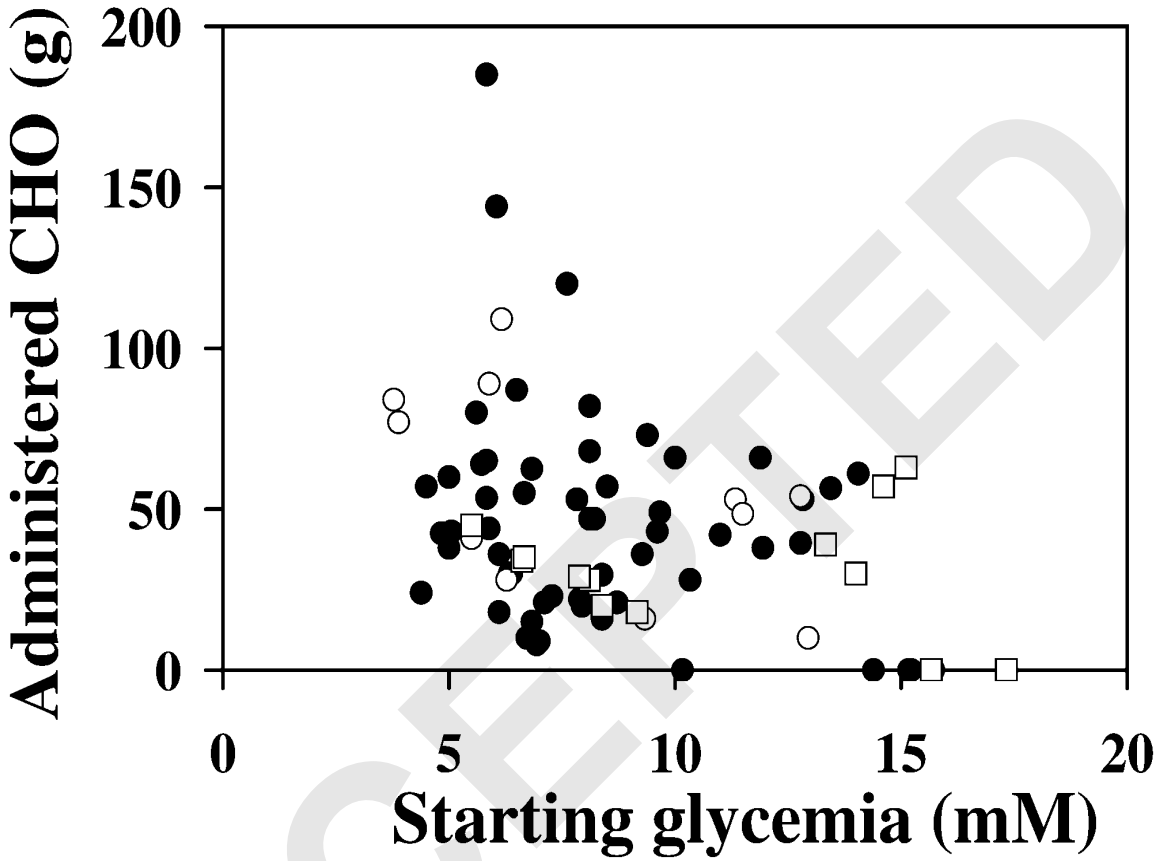

Figure 4

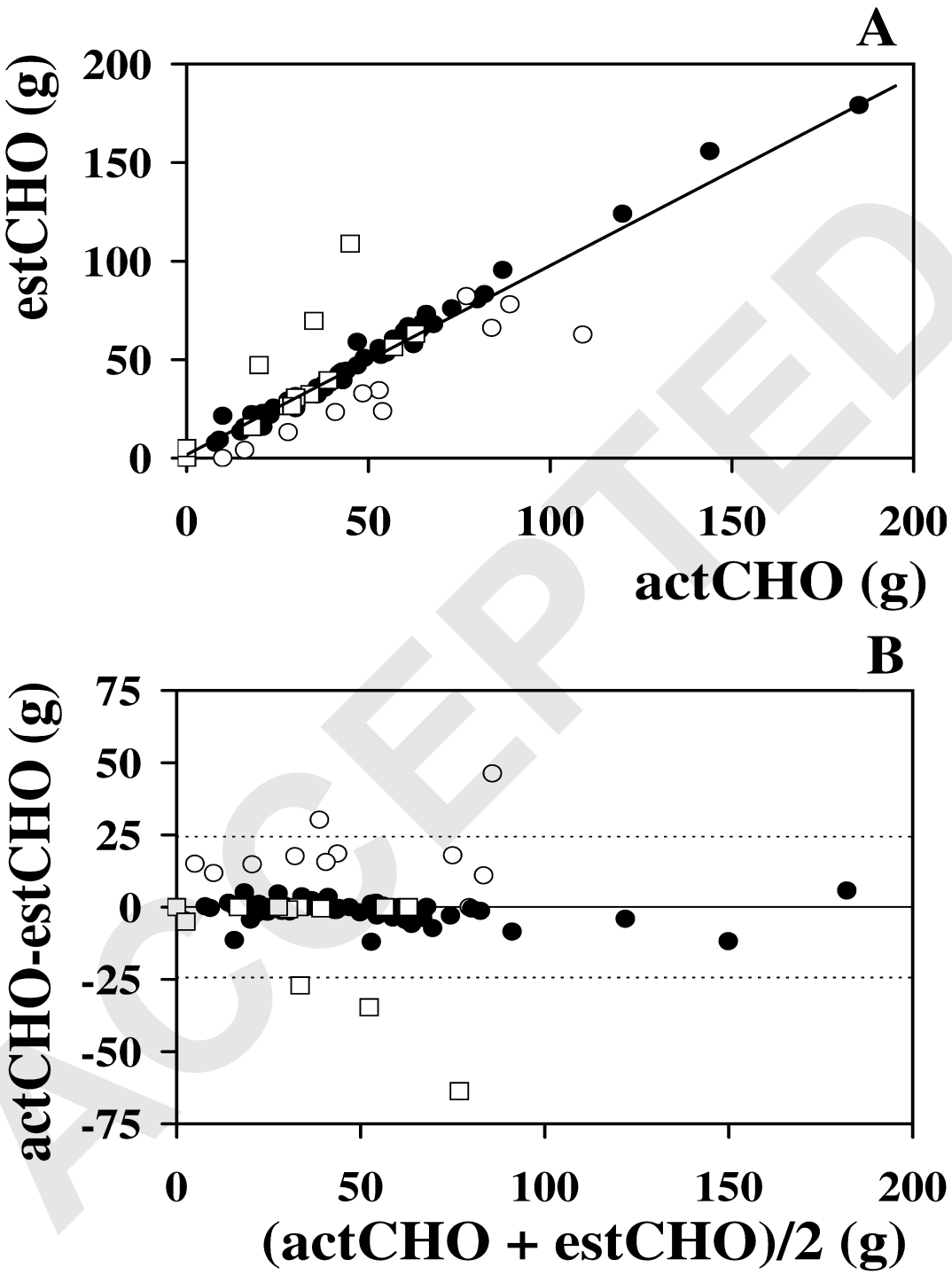

Figure 5

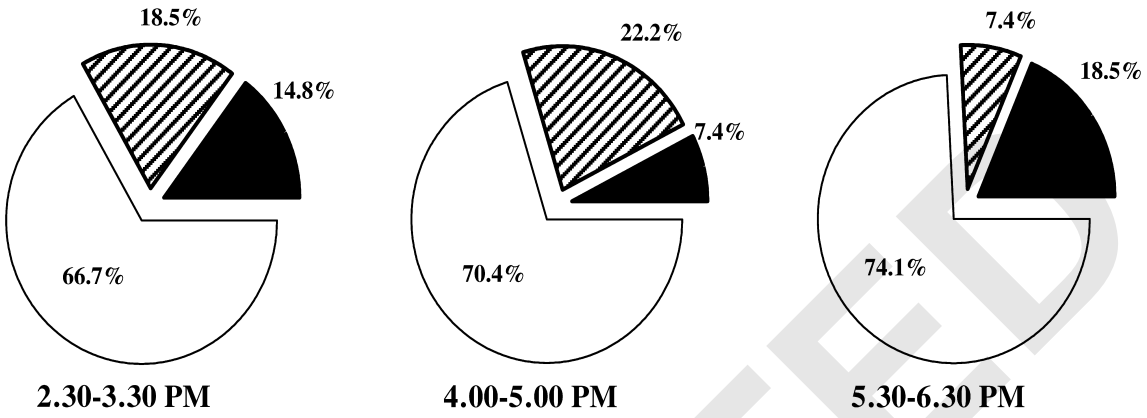

Table I. Glucose levels 30 min before, at the start and at the end of the walks.

	2.30-3.30 PM			4.00-5.00 PM			5.30-6.30 PM		
	-30'	**0**	**60**	**-30'**	**0**	**60**	**-30'**	**0**	**60**
INS group		**N = 4**			**N = 2**			**N = 5**	
	6.7 ± 4.2	6.8 ± 2.0	4.1 ± 1.2*	11.4 ± 0.1	11.6 ± 0.4	4.3 ± 0.4	8.0 ± 3.2	8.6 ± 2.8	3.8 ± 1.1*
	(3.8-12.8)	(5.3-9.6)	(3.2-5.8)	(11.3-11.5)	(11.3-11.9)	(3.9-4.6)	(5.5-12.9)	(6.3-13.2)	(2.5-5.5)
AD group		**N = 18**			**N = 19**			**N = 20**	
	8.9 ± 3.0	9.7 ± 2.8	7.2 ± 1.7	8.3 ± 3.2	9.0 ± 3.4	6.4 ± 1.6	8.4 ± 3.1	9.1 ± 3.0	6.5 ± 1.8
	(4.8-14.1)	(6.4-14.9)	(4.9-9.7)	(4.5-15.7)	(4.9-16.5)	(4.1-9.2)	(4.4-15.2)	(4.8-15.6)	(3.9-9.5)
EXC group		**N = 5**			**N = 6**			**N = 2**	
	11.7 ± 3.6	12.8 ± 3.7	13.0 ± 2.3§	9.8 ± 4.3	11.3 ± 3.6	11.2 ± 2.5§	12.7 ± 6.5	14.2 ± 4.4*	13.6 ± 1.1§
	(6.7-14.0)	(6.5-15.5)	(9.2-15.4)	(5.5-15.7)	(7.3-15.7)	(7.3-14.8)	(8.1-17.3)	(11.1-17.3)	(12.8-14.3)
All		**N = 27**			**N = 27**			**N = 27**	
	9.1 ± 3.5	9.8 ± 3.3	7.8 ± 3.2	8.8 ±3.4	9.7 ± 3.4	7.3 ± 2.8	8.7 ± 3.5	9.5 ± 3.3	6.8 ± 2.9
	(3.8-14.1)	(5.3-15.5)	(3.2-15.4)	(4.5-15.7)	(4.9-15.7)	(3.9-14.8)	(4.4-17.3)	(4.8-17.3)	(2.5-14.3)

Trials are grouped according to the time-scheduling they were performed and to the final evaluation. Data are averages ± standard deviations. Minimum and maximum values are in brackets. * Significantly different from AD group ($p < 0.05$); § Significantly different from AD group ($p < 0.001$)