Management of Exercise-induced Glycemic Imbalances in Type 1 Diabetes

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Abstract: Regular moderate-intensity exercise is strongly recommended for its beneficial effects in all people. In patients with type 1 diabetes, however, the exercise-associated glycemic imbalances remain an unresolved clinical challenge. Current guidelines require an in-depth understanding of the glycemic responses to exercise and each patient has to discover, by trial-and-error, his/her own strategy, several attempts being usually required to gain sufficient experience. Consequently, fear of hypoglycemia remains the strongest barrier to physical activity. This paper explores the potential strategies that may be employed to minimize the risk of exercise related glycemic imbalances. Moreover, a newly developed algorithm (ECRES, Exercise Carbohydrate Requirement Estimating Software) is described, which estimates on a patient- and situation-specific basis the glucose supplement required by the patient to maintain safe blood glucose levels. The algorithm was tested on 27 patients who performed three 1-hr constant intensity walks (each starting at a different time interval following insulin injection). Results showed that in 70.4% of the trials, independent of the time of day, the algorithm provided a satisfactory estimate of the carbohydrates needed by patients to complete the exercise with a glucose level within safe thresholds (i.e. 3.9 - 10 $mmol \cdot L^{-1}$). Despite the algorithm requires further experimental testing to be applied by the majority of patients, these results indicate 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 activities not planned in advance, thus allowing all insulin-dependent patients to safely enjoy the benefits of exercise.

Keywords: Carbohydrates, decision support system, hypoglycemia, insulin, metabolism, model.

INTRODUCTION

It is universally recognized that a healthy life style has also to include regular exercise. Regular moderate-intensity physical activity is strongly recommended also in patients with type 1 diabetes mellitus (T1DM) [1, 2]. Indeed, exercise improves insulin sensitivity [3, 4] and, associated with diet and insulin therapy, may help to achieve and maintain a better metabolic control [1, 5]. Moreover, exercise has protective effects against several cardiovascular risk factors [6-8] and can enhance quality of life by increasing self-esteem and psychological well being [9]. The exercise-associated glycemic imbalances, however, are often difficult to control and remain an unresolved clinical challenge for patients with T1DM [10]. Hypoglycemia during exercise can be dangerous and decreases performance; conversely, excessive snacking before or during exercise can result in hyperglycemia and negate some of the metabolic and cardiovascular benefits of exercise [11].

Exercise may have contrasting effects on patient's blood glucose level. Either a progressive rise [12, 13] or a decline [14-17] of glycemia have been observed, the more frequent acute complication of exercise being an excessive fall of glycemia [18] (below the hypoglycemic threshold of 3.9 $mmol \cdot L^{-1}$ [19]). So far only vague guidelines are available to patients with T1DM to minimize the risk of glycemic imbalances for activities performed at any time of day and under a wide range of intensities [1, 9, 18, 20]. These guidelines, however, require an in-depth understanding of the metabolic and hormonal responses to exercise and well-tuned self-management skills [1]. Each patient has to discover, by trial and error, his/her own strategy and several attempts are usually required to gain sufficient experience. Fear of hypoglycemia is still the strongest barrier to physical activity and the number of difficulties patients have to meet often further discourage them [21].

This paper first explores the potential dietetic and therapeutic strategies that may be employed to minimize the risk of exercise related glycemic imbalances. Subsequently, a newly developed algorithm (called ECRES, Exercise Carbohydrate Requirement Estimating Software) is described, which estimates on a patient- and situation-specific basis the glucose supplement required by the patient to maintain safe blood glucose levels, thus actually allowing patients to participate in sports and physical activities in a safe and enjoyable manner.

METABOLIC RESPONSE TO EXERCISE

Fatty acids and carbohydrates are the main substrates for energy production in skeletal muscle during aerobic exercise in well-fed humans, their relative contribution to total energy production being a function of exercise intensity [22-28]. Fatty acid oxidation rate is greater during mild- to moderate-

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intensity exercise [25]. Increases in power elicit a relative decrement in energy from fatty acid oxidation and a relative increment in glucose utilization [24]. Moreover, for the same absolute power, endurance training is associated with a decreased reliance on carbohydrate oxidation during the exercise [22, 29], with a concomitant increase in fatty acid oxidation [23, 30, 31]. Despite higher insulin levels throughout almost the whole day, patients with T1DM behave metabolically like healthy subjects during aerobic exercise, showing similar whole-body glucose oxidation rates as healthy people independent of the prevailing insulin concentration [14, 32-34], and in particular when the activity is performed under euglycemic conditions [35].

It is well established that a fraction of the carbohydrates used as fuel is taken from extracellular glucose [36, 37]. In healthy individuals, blood glucose homeostasis is maintained since insulin level suddenly decreases (contemporarily to a modest increase in catecholamine) thus allowing hepatic glucose production to match the increased glucose uptake by the exercising muscles [38, 39]. In comparison, patients with T1DM have lost the capability to endogenously decrease circulating insulin levels following exercise onset and thus their insulin concentration is independent of exercise and is set essentially by the time elapsed from the last exogenous insulin administration. Two main conditions may be identified: the first, when exercise is performed soon after insulin administration and the prevailing insulin concentration is rather high; the second, when the physical activity is performed after longer time intervals from insulin injection and the prevailing insulin concentration is low.

PATIENTS EXERCISING UNDER LOW PREVAILING INSULIN CONCENTRATION

From a physiological point of view, to avoid an excessive fall of glycemia, it would be logical to suggest patients exercising when the prevailing insulin concentration is low. Accordingly, to minimize the risk related to a too high insulin concentration, patients with T1DM are usually advised against exercise performed within 90-120 min of rapid-acting insulin administration [40].

Indeed, a lower risk of exercise-induced hypoglycemia was observed when low insulin levels prevailed (e.g. early in the morning before the morning insulin injection and breakfast) [41]. Nevertheless, it is worth remembering that under normal physiological conditions the liver is responsible for the extraction of a large (approximately 50%) fraction of the new insulin secreted by the pancreas (the so-called hepatic insulin clearance), leading to lower insulin concentrations at the periphery as compared to the liver [42]. In comparison, due to the subcutaneous administration of the hormone, patients with T1DM show quite the same insulin concentrations at the periphery and in the liver. Low insulin concentrations may be contemporarily unable to suppress hepatic glucose production [43] and insufficient to allow for the muscular glucose uptake. As a result, patients exercising under low insulin levels have to be aware that hypoglycemia may be prevented at the cost of an increased risk of hyperglycemia [18].

In addition, when patients exercise under low insulin concentration, the muscular glycogen stores are the only usable sources of glucose for energy production [14]. During the hours following the exercise, the greater muscular glucose uptake to replenish the glycogen stores [44] adds on the increased insulin sensitivity [45-47] and increases the risk of the so-called "postexercise late-onset" hypoglycemia [10] that may occur up to 24-36 hrs, in particular in sedentary patients who rely to a greater extent on glucose oxidation [22, 29, 48].

PATIENTS EXERCISING UNDER HIGH PREVAILING INSULIN CONCENTRATIONS

When T1DM patients exercise under high prevailing insulin concentrations, the inhibited hepatic glucose production cannot counterbalance the exercise-induced rise in muscle glucose uptake [9, 39, 49, 50], thus leading to the early-onset hypoglycemia. The mismatch between muscle glucose uptake and hepatic glucose production may be further exacerbated by a blunted counter-regulatory response due to antecedent exercise [51] or hypoglycemia [52-54].

To minimize the risk of an excessive fall of glycemia (in particular when exercise is within 90-120 min of a bolus), it would be logical to mimic the hormonal response in normal subjects by reducing the insulin dose before exercise [18, 40]. However, the amount of reduction remains in question. Recommendations for insulin dose reduction before moderate intensity exercise range from 25% [55] to about twice this percentage (i.e. 50-66% [56]). When exercise is more intense, a reduction up to 75-90%, depending on patients' usual regimen, has been suggested [55, 57]. Indeed, despite large reductions in the pre-exercise rapid-acting insulin dose, overall metabolic control appeared not significantly worsened [57] and the possible development of ketogenesis following exercise was not affected [58]. Reduction of the pre-exercise insulin dose, however, often is not sufficient to avoid an excessive fall of glycemia and thus patients are rarely exempted from a carbohydrate supplement [59, 60]. In addition, in many instances, after insulin dose reduction the improved glycemic profile during exercise was obtained at the cost of a raised plasma glucose level [55, 61]. This condition, however, does not always assure protection against subsequent hypoglycemia [59, 62]. Finally, changes in the insulin dose require the exercise both to be planned in advance and, thereafter, to be actually performed. Indeed, if for any unpredictable reason the patient abandons the idea of exercising, his/her glucose level will remarkably increase and worsen the metabolic control.

Furthermore, in many instances exercise is unexpected and the insulin dose cannot be modified ahead of time. In these cases, additional glucose ingestion is the only measure to prevent the exercise-induced lowering of glycemia [17, 18]. Carbohydrate supplements should include rapidly absorbable carbohydrates [18], but no clear-cut guidelines are available suggesting the appropriate amount needed to prevent an excessive fall of glycemia. Glucose ingestion equal to total-carbohydrate utilization was shown to attenuate the drop in glucose level during exercise in adolescents with T1DM, thus reducing the likelihood of hypoglycemia [17, 32]. Nevertheless, the authors do not suggest how to estimate the total-carbohydrate utilization (on an individual and situation-specific basis) making the extrapolation of these obser-

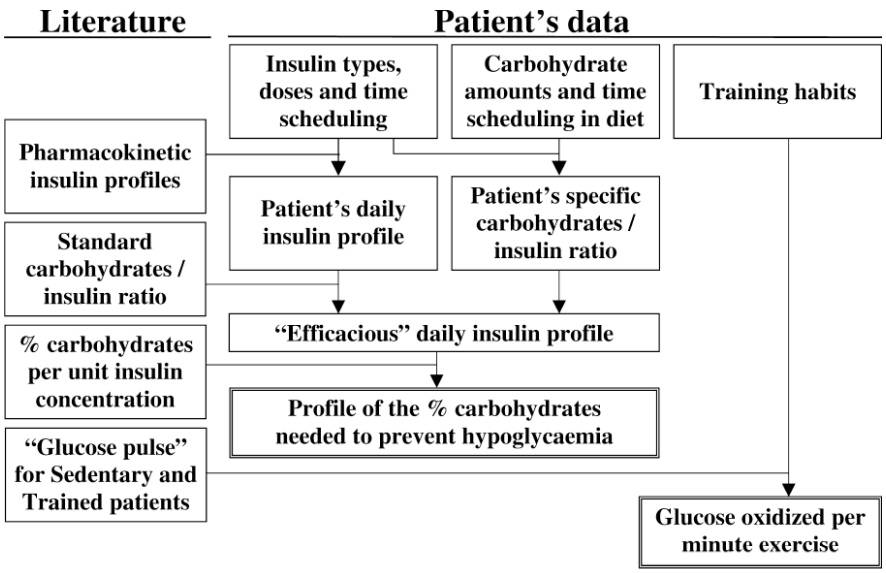

Fig. (1). Flow diagram of the first part (setting-up) of the ECRES algorithm [modified from 62]. The daily profile of the percentage burned carbohydrates needed to prevent hypoglycemia during exercise is estimated based on the patient's individual therapy (i.e. insulin types, doses, time scheduling and dietary carbohydrates). In addition, the glucose oxidation rates per minute exercise are calculated for all the heart rates ranging from rest to maximal heart rate for aerobic exercise.

vations into practice rather difficult [63]. Similarly, a general pre-exercise glucose supplement of 40 g was suggested to help patients in maintaining safe blood glucose levels during 60 min of moderate intensity exercise [16, 63]. After comparison of different strategies to prevent exercise-related hypoglycemic episodes, Grimm *et al.* [59] concluded that it is possible to prevent almost all these episodes (more or less independently of the insulin dosage adjustments) by adequately replacing the carbohydrates during the physical activity. Accordingly, the authors proposed an extra-carbohydrate table for different physical activities depending on exercise duration and intensity, the quantities ranging from 15 g to 100 g/hr exercise [59]. Indeed, the carbohydrate supplement represents an extra amount of energy introduced by the patient that may be counter-productive when purpose of exercise is weight control [64]. Nevertheless, in most cases the overall amount of energy spent during the exercise will be greater than the extra energy introduced with the carbohydrates supplement [62].

To oppose the exercise-mediated fall in glucose level, the performance of a single bout or intermittent high-intensity exercise has been proposed [65, 66] because of its effects on the counterregulatory hormones, which enhance the hepatic glucose production [67]. This type of exercise is typical of the activity patterns of many team field sports such as soccer or rugby, and also of spontaneous play in children [68]. This measure, however, has a limited use to shorter and less intense exercises [64] and may not be appropriate for sedentary, overweight or older individuals, for which a more constant activity in the aerobic range (e.g. walking) is recommended [69, 70].

Recent guidelines suggest that individualized strategies to limit glycemic imbalances associated with exercise can be initiated once total energy utilization has been quantified [71]. Simply quantifying total energy, however, may not be appropriate to counter an excessive fall of glycemia since glucose oxidation rate of a sedentary patient may be significantly higher as compared to that of an active patient [48].

A major limitation of most of the above-mentioned studies is that the observations have been carried out mainly at only one time interval following insulin administration. The amount of supplemental carbohydrates required to avoid hypoglycemia, however, is dependent on the prevailing insulin level, thus on the time distance from the last insulin administration [14, 18]. Moreover, exercise intensity and duration, and the level of glycemia before exercise are scarcely accounted for, while the influences of physical fitness and insulin sensitivity are even less examined [18].

A new algorithm (called ECRES, Exercise Carbohydrate Requirement Estimating Software) has been developed by our workgroup [62], designed to estimate, on a patient- and situation-specific basis, the amount of supplemental carbohydrates required by patients with T1DM before/during aerobic exercise to achieve end-exercise blood glucose levels between the hypoglycemic threshold of 3.9 $mmol \cdot L^{-1}$ [19] and the maximal random glucose target of 10 $mmol \cdot L^{-1}$ [72]. Main peculiarities of the algorithm are the following: 1) it is based on the patient's habitual regimen (i.e., 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) patient's physical fitness is considered when estimating the required amount of carbohydrates, 4) actual exercise intensity and duration are used for the estimate; and 5) the carbohydrate supplement can be calculated for any time of day the exercise is performed [62]. The following paragraphs aim at illustrating in some detail the algorithm and discussing the results of its preliminary application.

THE ECRES ALGORITHM

The algorithm first estimates the patient's daily total insulin concentration profile (Fig. **1**) on the basis of the usual

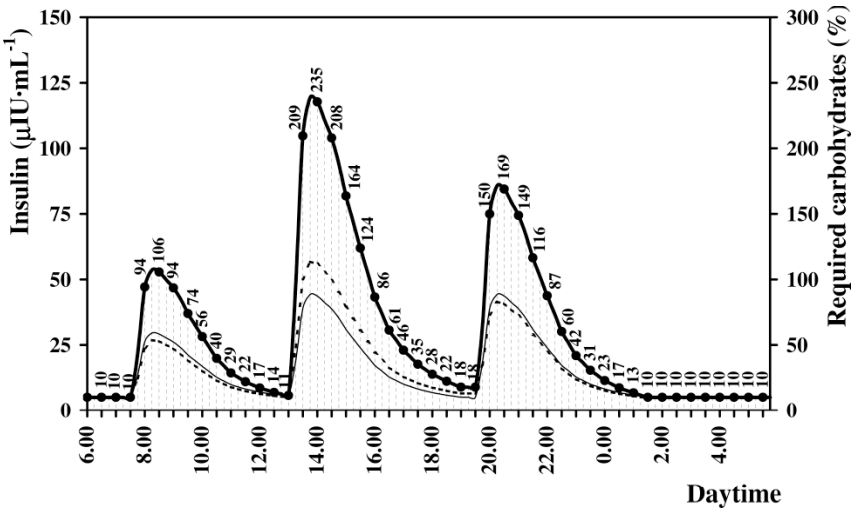

Fig. (2). Example for a typical patient of the percentage burned carbohydrates profile needed to maintain glucose level within the recommended range during exercise (thick line), the total insulin (thin line) and the "efficacious" insulin (hatched line). Data are plotted as a function of daytime (hrs). See text for details.
Uploaded therapy for a 70 kg body weight male patient (45 years old) was as follows: 7:30 AM breakfast (5 U Aspart, 40 g carbohydrates); 1:00 PM lunch (8 U Aspart, 80 g carbohydrates); 7:30 PM supper (8 U Aspart, 18 U Glargine; 60 g carbohydrates).

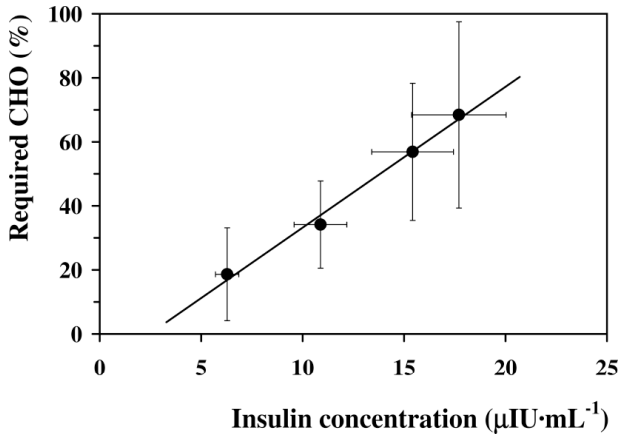

Fig. (3). The average percentage of burned carbohydrates (derived from alimentary and extracellular sources) is linearly related to the average insulin concentration (μUI·mL^{-1}) during the corresponding trial.

therapy and on "standard" pharmacokinetic profiles of insulin analogs reported by the literature [73-75]. To this aim the standard insulin profiles are realigned to the scheduled times of injection and scaled proportionally according to the ratio between the patient's dose and the standard dose for the specific insulin. Subsequently, in order to account for differences in insulin sensitivity among patients and throughout the day, the overall amount of insulin 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 computed, allowing to determine the patient's carbohydrates-to-insulin ratios for three daily time intervals (i.e., morning, afternoon and evening). An "efficacious" insulin profile is thus calculated (Fig. **2**) by multiplying the total daily insulin profile by the ratio between the patient's carbohydrates-to-insulin ratios for each day time period and the average carbohydrates-to-insulin ratio observed in our previous work (i.e., 4.8367 g/IU) [14]. Finally, each time point of the "efficacious" insulin profile is converted to the percentage of glucose oxidation rate required to maintain euglycemia. A linear relationship was observed by our workgroup between the prevailing insulin concentration and the glucose supplement needed to prevent hypoglycemia during moderate exercise [14]. Expressed as percentage of the overall glucose burned during the effort, these quantities were not significantly different from the percentages required for exercises of different intensity performed at the same day times (personal preliminary data, not yet published). The relationship between insulin concentration and percentage carbohydrates is thus determined pooling together all the data and is described by (Fig. **3**):

percentage carbohydrates

= 4.398 · insulin concentration – 10.76 (n = 4; R = 0.995).

The last step of the first part of the algorithm calculates the glucose oxidation rates per minute of exercise for all the heart rates ranging from rest to maximal heart rate for aerobic exercise (estimated as 70% of age-predicted maximum heart rate; the latter calculated as: 220 – age). This relationship was found to be statistically significant (Pearson's correlation coefficients being always higher than 0.90) in all our volunteers (n = 30). Different slopes were observed according to the individual's training habits (Fig. **4**), sedentary patients showing significantly higher glucose oxidation rates as compared to active patients ($p<0.001$). The overall relationships are described by:

glucose oxidation rate

= 0.504 · % maximal heart rate – 22.11 (n =36; R = 0.888)

and

glucose oxidation rate

= 0.679 · % maximal heart rate – 22.05 (n =29; R = 0.909)

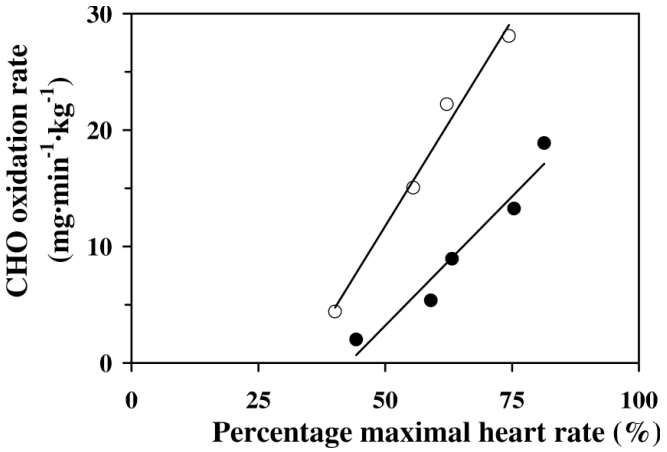

Fig. (4). Glucose oxidation rates ($mg \cdot min^{-1} \cdot kg^{-1}$) are plotted as a function of the corresponding percentage of maximal heart rate for an aerobically trained (full dots) and a sedentary patient (open dots). For the same relative exercise intensity, the aerobically trained patient shows lower values as compared to the sedentary one.

for active and sedentary patients, respectively (the glucose oxidation rate being expressed in mg min^{-1} per unit body mass) [48].

The second procedure of the algorithm (Fig. **5**) has to be run on each exercise occasion and allows to actually estimating the amount of supplemental carbohydrates according to the characteristics of the exercise (i.e. intensity, duration, starting time of day) and the metabolic conditions (i.e., glucose level). The overall amount of glucose oxidized during the effort is first calculated on the basis of the expected exercise intensity (defined by heart rate) and duration. Subsequently, the appropriate percentage of carbohydrates needed to prevent hypoglycemia is selected according to the time of day the exercise is performed and the time elapsed from the last insulin injection. This percentage is then applied to the overall amount of glucose burned, yielding the theoretically amount of supplemental carbohydrates. 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 algorithm is able, optionally and for the specific exercise occasion, to estimate the carbohydrate supplement according to the varied insulin dose. Finally, the amount of excess/lack glucose solved in the body is computed as the product between the difference between actual glycemia and the theoretical glycemia the patient should have at the time of exercise, and the extra cellular fluid volume, in turn estimated as 0.27 $L \cdot kg^{-1}$ in men and 0.225 $L \cdot kg^{-1}$ in women [76]. The excess/lack glucose solved in the body is then subtracted/added to the theoretically estimated supplement, ultimately yielding the amount of carbohydrates to be actually consumed.

A rough estimate of the additional carbohydrates needed to prevent late-onset glycemic imbalances is also calculated as the difference between the overall amount of glucose oxidized during the exercise and the amount of carbohydrates required to maintain glycemia near the normal level during the effort.

PRELIMINARY EVALUATION OF THE ECRES ALGORITHM

Twenty-seven patients with T1DM (19 men, 8 women; aged 44 ± 11 years; Body Mass Index 24 ± 2 $kg \cdot m^{-2}$; diagnosed with type 1 diabetes 22 ± 11 years before experimentation; average HbA_{1c} 7.2 ± 1.1%) were recruited to participate to a preliminary evaluation of the ECRES algorithm [62]. All patients were on a basal-bolus insulin regimen, were not affected by other chronic diseases, and had no evidence of diabetes complications contraindicating physical

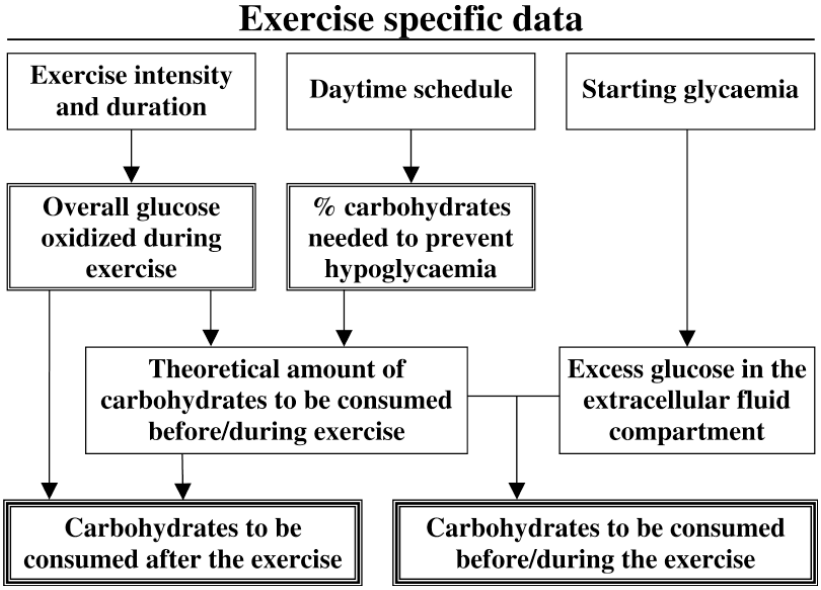

Fig. (5). Flow diagram showing how the algorithm estimates at each exercise occasion a) the actual amount of carbohydrates the patient has to consume before/during exercise and b) the additional carbohydrates needed to prevent late-onset glycemic imbalances [modified from 62]. The calculation is based on the exercise specific data (i.e. intensity, duration and starting time of exercise) and on the glucose level at the start of the activity.

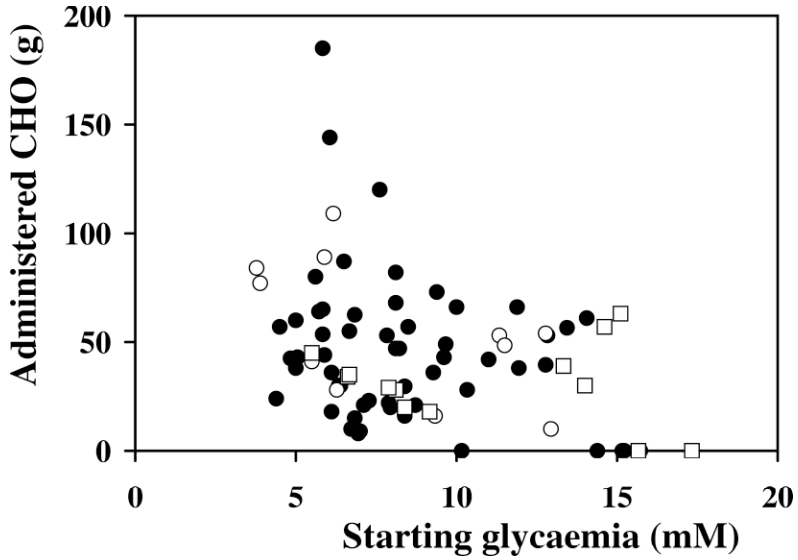

Fig. (6). Actual delivered supplemental carbohydrates (g) are plotted as a function of starting glycemia (mM).
Full dots: walks concluded with glycemia within the selected thresholds (i.e. 3.9 - 10 mmol·L^{-1}).
Open dots: walks requiring the administration of additional amounts of carbohydrates.
Open squares: walks concluded with a too high glycemia (>10 mmol·L^{-1}).
Reprinted from [62]

activity. Volunteers were classified according to the self-reported physical activity habits as "active" (12M, 7F), who exercised regularly at least 30 minutes for 3 days/week, and "sedentary" (7M, 1F), who exercised only occasionally. Patients were advised to refrain from unusual physical activities 24 h prior to the walks, to maintain their usual diet and insulin regimen, and to control their blood glucose levels according to the self-management procedures in order to avoid the occurrence of hypoglycemic events. Each volunteer repeated a constant intensity aerobic treadmill walk of one-hour duration three times, each time starting at different time intervals (90 min, 180 min, and 270 min) following the lunch (midday) insulin treatment. Half an hour before the start of the walk, patients were administered (in the form of sugar or sugar-drops) approximately 70% of the amount of carbohydrates estimated by the ECRES algorithm. The remaining fraction (30%) of the estimated carbohydrate requirement was administered during exercise only if glycemia was within the recommended range and other additional known amounts of sugar were given if glycemia fell below 5.0 mmol·L^{-1}.

Glycemia (determined by means of appropriate reactive strips; Accu-Check^{TM} Active, Roche Diagnostics, Switzerland) fell significantly ($P < 0.01$) from 9.6 ± 3.3 mmol·L^{-1} at the start to 7.3 ± 3.0 mmol·L^{-1} at the end of the walks. Interestingly, starting glycemia was not related to the administered carbohydrates (Fig. **6**). Supplemental carbohydrates, however, were significantly different for the exercises starting at the three different times of the day ($P < 0.001$), amounting on average to 63 ± 28 g, 44 ± 35 g and 24 ± 23 g, respectively. More importantly, the amounts of supplemental carbohydrates estimated by the ECRES algorithm were not significantly different from the actual administered ones.

The following three grouping criteria were then applied to the walks: 1) the amount of carbohydrates estimated by the ECRES algorithm was insufficient and additional amounts of sugar had to be administered; 2) the amount of carbohydrates estimated by the algorithm was excessive and was not completely administered; 3) the amount of carbohydrates estimated by the algorithm was adequate to allow patients ending the exercise with the glucose level between the hypoglycemic threshold of 3.9 mmol·L^{-1} [19] and the maximal random glucose target of 10 mmol·L^{-1} [72]. Altogether, 13.6% walks required greater amounts of carbohydrates as compared to the quantities estimated by ECRES (Fig. **7**); at the other extreme, in 16.0% of cases the supplemental carbohydrates estimated by ECRES were overestimated; the remaining 70.4% walks satisfied the third criterion, i.e., the carbohydrates estimated by the algorithm allowed patients to end the exercises with the glucose level within the selected thresholds. The percentages of walks assigned to the three categories were not significantly different among the three times of day the exercises were performed [62], suggesting that the algorithm is able to estimate the supplemental carbohydrates requirement with similar precision for any time throughout the day the exercise is performed.

Despite a rather regular life style and plenty of attention to glycemia, patients often experience unexplainable hypoglycemic or hyperglycemic events, which are the consequence of unexpected and unpredictable events temporarily affecting patient's insulin sensitivity. A hypoglycemic event occurring in the hours preceding the exercise is believed to significantly influence the glycemic response to the effort [52-54]. In our experimentation, patients were accepted also if they had experienced a hypoglycemic event during the preceding 24-48 hours. Consequently, we could make up a "hypoglycemic" group by collecting the walks performed following a hypoglycemic event (n = 42), the remaining cases constituting an "euglycemic" group (n = 39). Comparison of these two groups showed that glycemia at the start and at the end of the walks was signifi-

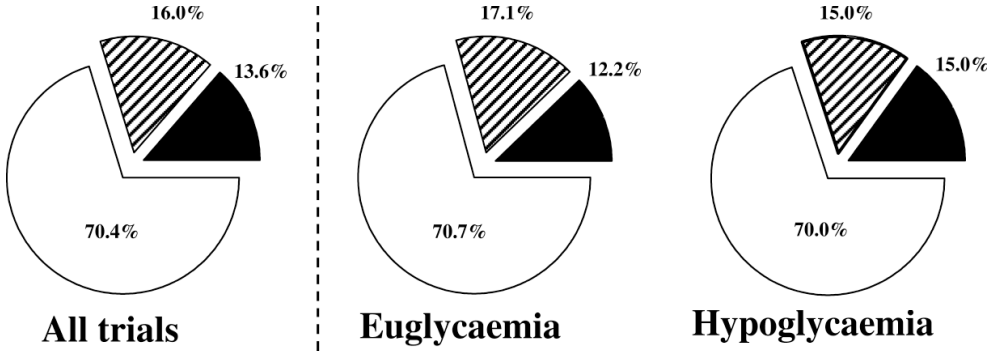

Fig. (7). Percentage walks are illustrated for all the trials and for the euglycemic and hypoglycemic groups. No significant difference was found among the three groups.
Open slice: walks concluded with glycemia within the selected thresholds.
Full slice: walks requiring the administration of additional amounts of carbohydrates.
Hatched slice: walks for which the amounts of carbohydrates estimated by the algorithm were not fully administered.

cantly lower in the "hypoglycemic" group as compared to the "euglycemic" 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; $P <$ 0.005). The fall of glycemia during exercise and the amounts of supplemental carbohydrates, however, were not significantly different between the two groups. More importantly, the percentage trials assigned to the three categories (according to the amount of administered carbohydrates) was not significantly different (Fig. **7**).

A further analysis revealed that, in five cases requiring a greater amount of supplemental carbohydrates as compared to the quantities estimated by the ECRES algorithm, a hypoglycemic event occurred in the 3-4 hours just preceding the exercise. A transiently enhanced insulin sensitivity may explain either the hypoglycemic events and the increased carbohydrates requirements. At the other extreme, six walks out of those for which the estimated carbohydrates requirement was too high, 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 this condition.

Supplemental carbohydrates for the preliminary evaluation of the ECRES algorithm were given in the form of sugar/sugar drops. Different types of carbohydrates (e.g. starches) or the contemporary consumption of fats or proteins would likely result in a different glycemic response. The risk of exercise-induced hypoglycemia may thus continue until glucose is completely absorbed, while glycemia at the end of exercise may be high. Accordingly, carbohydrate supplements should mainly include rapidly absorbable carbohydrates [18], as was done in our experimentation.

MAIN CAUSES OF ERROR IN THE USE OF THE ECRES ALGORITHM

The incorrect assignment of the patient as "sedentary" or "active" is one of the major sources of error in the estimate of the required amount of carbohydrates by means of the ECRES algorithm. Moreover, some patients are even more trained than expected by the available equations, which estimate the glucose oxidation rates [48], thus yielding too high estimated glucose supplements. The error in the estimate of the overall amount of glucose burned during the effort, however, can be negligible when 1) the exercise is performed at low intensity, corresponding to a low overall amount of glucose burned, and 2) the activity is performed at least 3-4 hrs following insulin administration, i.e., when the fraction of the burned glucose required to maintain euglycemia (as calculated by the algorithm) is low because of the low insulin concentration. In turn, for early post-prandial exercise (i.e., starting within 60-90 min from the last meal), the erroneous assignment of the patient as "sedentary" or "active" may be crucial. Undoubtedly, a more precise classification of patients' fitness level will likely enhance the performance of the algorithm and reduce the possible related error. The estimated requirements will likely be improved also by uploading in the algorithm the patient's personal "glucose pulse" data (i.e., his/her own relationship between heart rate and glucose oxidation rate), rather than using average equations as the present version of our algorithm does.

The algorithm uses the ratio between the amount of dietary carbohydrates and usual insulin dose to describe the patient's insulin sensitivity. In our experience, this is actually true if and only if patient's 1-h postprandial glucose level is about 1.7-2.8 mmol · L^{-1} higher than the corresponding preprandial level [77]. The so calculated ratio is greatly affected by even small changes in the amount of carbohydrates habitually consumed with diet, that consequently affect also the estimate of the supplemental carbohydrates needed for exercise.

The use of the ECRES algorithm requires patients to predict exercise intensity and duration (i.e. the main parameters to estimate the overall amount of glucose burned during the effort). Patients may get wrong in predicting these quantities. However, similarly to the erroneous classification of patient according to his/her fitness level, the error may be negligible when the exercise is performed at low intensity, and late after insulin administration, whereas it may be of greater importance for higher intensity and/or early exercise. The relationships between heart rate and glucose oxidation rate (see above) allow calculating that a 5 beats per minute error in the predicted exercise intensity for a 70-kg body weight sedentary patient (the worst case) who will exercise for 1 hour, yields an overall error of 8.4 g in the estimated overall amount of glucose burned (0.002 g per minute per kg body

mass). To avoid an excessive fall of glycemia, however, only a fraction of the overall amount of glucose burned is usually required, depending on the time scheduling of the exercise. In addition, several commercial heart rate monitors allow to continuously verifying actual heart rate by wearing a simple elastic belt. After a few minutes of activity, patients can thus recalculate the correct requirement (see below the possible implementations of the algorithm); moreover, according to common security behaviours for patients with T1DM, they have always to bring some sugar with them, in particular during the physical activities.

Finally, it is well known that also a single bout of exercise has an insulin sensitizing effect. The latter, however, is short-lived and disappears after about 48 h [78]. Despite the underlying biological mechanisms have been studied in some detail, no precise data are available on the consequent possible reduction in insulin doses in patients with T1DM. Patients are thus advised to maintain their usual insulin regimen during the 24-48 hours after a single exercise bout and only in rare cases reductions of the long-lasting insulin dose at the first occasion are suggested. Accordingly, the ECRES algorithm does not specifically take into account the impact of a recent single exercise bout. In contrast, repeated physical activity (i.e. exercise training) results in a persistent increase in insulin action in skeletal muscle [78] that is reflected in lower insulin doses for the usual therapy, main parameter for the estimates. Regularly exercising patients may in any case take advantage of the algorithm to face glycemic imbalances for physical activities performed outside their usual training hours, when there is less experience about the metabolic response to exercise.

DISCUSSION

All patients with diabetes should have the opportunity to benefit from the many valuable effects of exercise. So far, however, no clear-cut guidelines have been proposed to help patients with T1DM maintaining a near physiological glycemia for activities performed at any time of day and under a rather wide range of intensities. Only too general strategies have been suggested [1, 9, 18, 20, 55, 57], 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.

Results of the preliminary application of the above-described algorithm [62] are very promising. Independent of the time distance from the insulin injection and without requiring any time-consuming trial-and-error approach, the carbohydrates requirement estimated by the algorithm would be adequate to prevent immediate exercise-induced glycemic imbalances in about 70% of the 81 walks performed by the patients [62]. Furthermore, it can be foreseen that, avoiding or appropriately taking into account the major causes of error, the amount of supplemental carbohydrates estimated by the algorithm will be adequate for an even higher percentage of cases. This algorithm [62] has thus the potential to become a very useful 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 (i.e. during exercise) exercise-induced glycemic imbalances independent of the time of day the activity is performed. Indeed, 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 use of the algorithm will allow patients to easily determine the amount of carbohydrates they need for the exercise and thus safely enjoy all the benefits of physical activity, in particular if it is spontaneous and not planned in advance, or in patients whose fear of hypoglycemia is particularly strong, maybe because of their difficulties in understanding the metabolic and hormonal responses to exercise. Patients who exercise regularly 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 lower usual insulin doses, which are main parameters to calculate the supplement.

Unfortunately, an excessive fall of glycemia may occur also up to 24-36 hrs after the end of the exercise (the so-called "late-onset hypoglycemia" [10]). These episodes are due to the increased glucose uptake after exercise that serves to support repletion of muscle glycogen stores [44, 79]. They may be even more dangerous than the immediate hypoglycemia since they frequently occur at night [11, 80]. To counter the late-onset hypoglycemia, the addition of bouts of intermittent high-intensity exercise was investigated, but contrasting effects were observed [81, 82]. Research studies that could provide an evidence-based framework to guide management of late-onset hypoglycemia are lacking and, consequently, no clear-cut guidelines are to date available to assist patients in arranging extra amounts of carbohydrates and/or changes in the insulin doses after an exercise session. We plan to investigate this problem in the near future and, subsequently, to enhance the features of our algorithm.

Several different implementations of the ECRES algorithm can be foreseen, each being characterized by different pros and cons. An implementation on desktop computer and/or on a specific handheld device can be hypothesized for a direct patient's use. The required electronic circuits, however, can also be easily integrated in many different devices, e.g. training equipments or glucose monitoring systems. Finally, we believe that a real-time version of the algorithm, implemented on a portable device and able to estimate during exercise the supplemental carbohydrates used on the basis of actual heart rate (acquiring data like the commercial heart rate monitors do), will be useful to warn patient during the exercise of the actual risk of hypoglyceamia. This solution will remove the need for patients to estimate exercise intensity and duration (only glucose level before exercise and the amount of supplemental carbohydrates consumed remains to be loaded in the device on each exercise occasion). Such a device may be of very simple use, releasing patients from the need of understanding in some detail the metabolic responses to exercise, and thus it might become a very intriguing device.

Finally, although the amount of the carbohydrates supplement is estimated on a patient- and situation-specific basis, dramatically reducing the time spent for the trial-and-

error approach, the algorithm represents only a Decision Support System. In fact, unpredictable factors may influence patient's usual insulin sensitivity (as already stated above) and thus the glycemic balance. Consequently, the use of the algorithm does not completely exempt patients from common security behaviours, e.g., controlling their glucose level according to the usual procedures and bringing always some sugar with them during the physical activities. In addition, in order to safely apply the algorithm on a wide proportion of the diabetic population, further research is needed to evaluate the performance of the algorithm also for different exercise intensities, durations and modalities.

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