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Conference Report

Managing insulin therapy during exercise in Type 1 diabetes mellitus

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Abstract. *Background:* Exercise is integral to the life of T1DM subjects. Several factors influence the metabolic response to exercise in these patients. Despite physical and psychological benefits of exercise, its hypo- and hyperglycemic effects may cause discouragement from participation in sports and games. *Aim:* To use existing evidence from literature to provide practical indications for the management of insulin therapy in subjects with T1DM who practice sports or physical activities. *Methods:* Bibliographic research was performed on PubMed and the main Systematic Review and Guidelines database were also searched. *Results:* Existing guidelines are useful but the exact adjustments of insulin dose must be made on an individual basis and these adjustments can be made only by "trial and error" approach. *Conclusions:* These clinical indications may be a starting point from which health care providers can find practical advices for each patient. (www.actabiomedica.it)

Key words: Type 1 Diabetes Mellitus, exercise, physical activity, pump, intensive insulin therapy, glycemic response, hyperglycemia, hypoglycemia, glucose counter-regulation

The triad of insulin, diet, and exercise has been the basis for treatment of Type 1 Diabetes Mellitus (T1DM) for the past 80 years. Regular physical activity has been known to improve health and behavioral outcomes in children and adolescents (1). In particular, in children and young people with T1DM, exercise may have beneficial effects on metabolic control, body weight, blood pressure levels (2), self-concept, peer group interaction and quality of life (3-7). However, in subjects with T1DM, managing physical activity may be difficult due to the exogenous insulin administration and to the necessity of following an intensive insulin regimen in order to reduce the incidence of long term complications (8). The most frequent and dangerous consequence of physical exercise in T1DM subjects is hypoglycemia during exercise and up to 12 - 24 hours afterwards (9, 10). The natural and physiological decline of serum insulin during exercise, indeed, cannot occur in T1DM patients. As a consequence, glucose production in the liver cannot be activated during exercise and marked hypoglycemia may occur. Experiencing hypoglycemia may be a source of anxiety for young people with T1DM and their families. It may be the cause of embarrassment with peers and eventually discourage sport activity (11). It is also possible that, even in well-controlled patients, physical activity may lead to hyperglycemia secondary to sympathetic nervous system activation with potential risk of ketosis (12, 13). Several factors influence the metabolic response to exercise in patients with T1DM: duration and intensity of exercise, level of metabolic control, type and dose of insulin administered before exercise, site of injection, timing of previous insulin injection and food intake relative to the exercise.

This paper focuses on two issues: on one side the intrinsic variability of substitutive insulin therapy

(with regard to the physical state of insulin, to the injection site, to the modes of administration); on the other side the consequences of hypo- and hyper-insulinization. The goal of this paper is to use existing evidence from literature to provide practical indications for the management of insulin therapy in subjects with T1DM who practice sports or physical activities.

Methods

Bibliographic research was performed on PubMed from 1970 to 2006, combining the following MeSH terms: "Diabetes Mellitus, Type 1", "exercise", "motor activity", "blood glucose", "hyperglycemia", "hypoglycemia", "insulin", "glucose", "Insulin Infusion Systems". The main Systematic Review and Guidelines Database (Cochrane, SIGN, NICE, APEG, National Guidelines Clearinghouse, ADA, ISPAD) were also searched. The work was completed with hand searching of articles on non-indexed journals, and using the references of retrieved papers.

Factors influencing the organism's response to insulin therapy

Effects of physical state of insulin, injection volume and absorption variability

It is necessary to point out that a major difficulty in managing insulin therapy is the low reproducibility of metabolic effects of the subcutaneous injection.

Subcutaneous injections of identical insulin doses may lead to considerable intra-individual and inter-individual differences in the current metabolic control. This variability is higher with intermediate or long-acting insulin preparations, compared to regular insulin. This intra-individual variability is responsible for more than 80% of the day-to-day fluctuation in blood glucose levels. Besides this, the absorption of intermediate-acting and long-acting insulin is dose-dependent with a decreasing absorption rate with increasing dose of insulin (14-16).

Continuous subcutaneous insulin infusion reduces the intra-individual variability of absorption as insulin is administered in the same site for the duration of the subcutaneous cannula (17, 18).

Effects of injection site and injection technique

Both the technique and the site of insulin injection influence the absorption rate.

Areas where subcutaneous layer is thin - like the upper arm - are not recommended because of increased risk of intramuscular injection. Administering insulin in the muscle induces a marked increase in insulin absorption and a substantial fall in plasma glucose (19). Lean individuals have an increased risk of accidental intramuscular injections. This can be minimized by using a two finger pinch technique, an injection angle of 45 degrees and 8 mm needles (20, 21). Subjects who practice physical activity should also avoid administering insulin in body parts which are involved in the movement. The study of effects of leg exercise on insulin absorption from various injection sites of labeled rapid insulin evidenced that injection in arm or abdominal sites reduces exercise-induced hypoglycemia by 57% and 89% respectively, compared to leg injections (22). As far as NPH o zinc suspended insulin are concerned, physical exercise doesn't determine changes in their absorption, unless they are mixed to rapid insulin or short-acting analogues (23). Similarly, subcutaneous thigh injection of labeled insulin glargine during an exercise which involved mainly legs did not determine an increase of its absorption (24). With regard to injection site, patients should be advised to rotate within the same site, instead of using different sites. This makes it easier to anticipate the type of glycemic response to insulin administration, and makes the management of exercise more comfortable (25).

Insulin absorption is also conditioned by environmental conditions in which physical activity is performed. In hot and moist ambient conditions, absorption may be increased and further reduction in insulin dose may be required (17, 26, 27). Very low temperatures, like in winter sports, may cause a reduced absorption of insulin from injection sites, or they may even lead the insulin into the pump or that into pen injectors to freeze. This can determine an unexpected increase in blood glucose levels (28).

In summary, attention should be given to
- avoiding intramuscular injections
- giving proper advice about injection site
- rotating the injection site within the same area
- taking into account environmental conditions

Managing insulin therapy to prevent acute complications

The insulin level is an important determinant of the metabolic response to exercise in patients with T1DM (3). A major problem for people with T1DM is that plasma insulin concentration does not decrease during exercise as in normal subject. On the opposite, it may even increase first due to enhanced absorption, secondly due to increased insulin sensitivity and finally when exercise is undertaken shortly after insulin injection (especially rapid analogous) (29). Consequently, the ability to mobilize fat and carbohydrate fuels for exercise may be compromised: this facilitates the onset of hypoglycemia during and after exercise (3). Besides this, the hypoglycemic counter-regulatory mechanism can be less active and responsive, and this may result in severe hypoglycemia (30). It is therefore paramount that during exercise a certain level of circulating insulin should be maintained in order to prevent both overinsulinization and underinsulinization (31).

Overinsulinization

Since during exercise insulin levels are elevated in the patient with T1DM, both glycogenolysis and gluconeogenesis are inhibited. A patients may have a slight reduction of serum glucose or a symptomatic hypoglycemia in according to intensity and extent of exercise (32). The lag effect of exercise may cause a fall in blood glucose long after its completion, and even as long as the morning after exercise that has taken place during the evening (33). Therefore, performing exercise with normal insulin dose and no additional carbohydrate significantly increases the risk of hypoglycemia during and after exercise (34). The amount of reduction in insulin dose will depend on the duration and intensity of exercise being performed, insulin and glycemic level before exercise, the time of day, environmental conditions, training status, habitual or unaccustomed extent of exercise, emotional stress or excitement (25, 35).

In children and adolescents, exercise is often spontaneous and unplanned: this means that it is not always possible to anticipate the need to adjust the insulin dose. In this case it may be useful to take supplemental carbohydrates before, during and/or after exercise (3, 21, 26). However, low-level activities generally do not affect blood glucose levels unless activities are performed for more than 10 min (33). An unplanned exercise is easier to manage in patients with insulin pumps, as the administration of insulin can be easily stopped by simply disconnecting the device (17, 18).

When exercise is planned and performed in the post-meal period, it is important to adjust the pre-meal insulin dose, particularly if exercise is expected to be intense or prolonged (33). An aspect which may make the insulin dose management more difficult is that moderate intensity phases alternate to high intensity phases of game which generally have a short duration - as in many team sports - do not necessarily imply significant modification to insulin doses. The increase of circulating levels of catecholamine and growth hormone induced by intermittent high-intensity exercise would justify the theoretical lower risk of hypoglycemia (36, 37).

If exercise is performed in the morning before pre-breakfast insulin administration, the risk of hypoglycemia is reduced compared to other times of the day because 1) circulating insulin is low and 2) liver and muscle glycogen stores are filled (28, 38).

In general, the use of insulin analogues (short- and long-acting) both in multiple injection basal-bolus regimen and in subcutaneous infusion by pump may offer significant advantages in terms of hypoglycemia avoidance (16, 24, 39, 40, 41). Even with an appropriate reduction in the pre-exercise insulin dose, over-insulinization can still occur during or shortly after exercise because contractions make the muscle more sensitive to insulin. Late onset hypoglycemia can still occur despite appropriate insulin reduction, secondary to persistent increase of insulin sensitivity and to mandatory repletion of muscle glycogen stores (9, 42).

Vicious circle of exercise and hypoglycemia

Managing insulin therapy in prevision of physical exercise, should take into account the occurrence of hypoglycemic episodes or of the performance of physical activity in the previous 12-24 hours. After an episode of hypoglycemia or exercise, indeed, counterregulatory responses to hypoglycemia are reduced, making hypoglycemia itself more likely to occur. This phenomenon, defined as "hypoglycemia-associated autonomic failure," has been documented even in healthy subjects (43).

This vicious circle is more accentuated when previous hypoglycemia was deep and/or prolonged and the previous physical activity has been intense. In these conditions the hypoglycemic counter-regulatory mechanism can be blunted up to more than 50% (30, 33, 43, 44). This phenomenon requires a particular attention in the management of insulin therapy in tightly controlled patients and in patients with autonomic neuropathy. The former will have lower blood glucose levels before epinephrine and other counter-regulatory mechanisms are activated, increasing the risk of severe exercise induced hypoglycemia (32); in the latter, besides a reduced perception of hypoglycemia symptoms, the diabetic autonomic neuropathy further reduced responses of adrenaline to hypoglycemia independently of recent antecedent hypoglycemia (30, 45, 46).

Underinsulinization

Patients with poor glycemic control who have insulin deficiency can easily develop hyperglycemia with or without ketosis as a consequence of exercise. Indeed, even in well-controlled patients with adequate insulinization, high intensity exercise may cause hyperglycemia due to an increase in catecholamines and sympathetic nervous system activation of hepatic glucose production which exceeds the rate of glucose utilization (13, 42, 47, 48). For this reason, if blood glucose is higher than 250 mg/dl and ketosis is present, exercise should be delayed and supplemental insulin dose should be given. Exercise can start once metabolic condition is normalized. On the other hand, since circulating insulin cannot increase after work, even a slight pre-exercise hyperglycemia without ketosis may need small doses of supplemental insulin injection in order to prevent blood glucose levels to increase to higher levels in the post-exercise phase (23, 32).

Modifying insulin therapy according to exercise

"It is impossible to provide a single set of guidelines appropriate for all people with diabetes who wish to exercise, and the best advice is to encourage diabetics to document for themselves what works and what does not work" (35).

Since this paper has been published, a lot of studies and recommendations about insulin and exercise have flourished (1, 9, 27, 28, 32, 33). Nevertheless, these indications seem difficult to be applied to daily diabetes management, as they strictly depend on the specific conditions considered in the studies performed (type and extent of exercise, age and metabolic control of studied subjects, type of insulin and insulin scheme). However some general indications can be derived from these studies and they can be summarized as follows

Exercise performed early in the morning before breakfast:

- reduce the evening injection of intermediate or long acting insulin by 20-50%, according to intensity of exercise (38);
- it may be advisable to reduce the evening dose of long-acting insulin analogues (24);
- it may be also useful to reduce the pre-breakfast insulin dose by 30-50% (27).

Exercise performed in the postprandial phase:

- delay activity for at least 1-2 hours after premeal insulin administration(32);
- reduce pre-meal insulin dose by 20-75%, according to intensity and extent of exercise (9);
- it may be useful to reduce insulin dose before the next meal (9, 34);
- reduce premeal insulin dose by 70-80% if exercise extent is up to 90 min in duration (28).

Prolonged exercise:

- reduce premeal rapid insulin dose by 30-50% if exercise lasts up to 4 hours;
- reduce the previous evening injection of basal

insulin by 50% and reduce rapid insulin doses by 30-50% during and after exercise if an all-day walking is anticipated;
- reduce the evening basal insulin dose by 10-20% up to 24 hours after an all-day exercise(33).

Intermittent high-intensity exercise – team sports:
- reduce premeal insulin by 70-90% (27);
- it may be not necessary to reduce premeal insulin if team game lasts less than 60 min (36, 37).

Using pump

Postprandial exercise:
- reduce the pre-meal bolus, if exercise starts within 1-3 hours from meal (49);
- decrease the basal rate by 50% for the duration of exercise (49);
- it may be useful to start the basal rate reduction 30-60 min before starting exercise (49);
- modification of basal rate infusion will induce its effects after a delay of 2-3 hours (17)
- instead of reducing basal rate, the pump can be switched off or disconnected (50);
- putting pump in suspend mode may cause clog in the infusion set (49)
- take supplemental bolus before and/or during suspension of infusion if suspension lasts up to 2 hours (49).

Avoiding late onset hypoglycemia:
- Reduce overnight basal insulin delivery by 10-30% (1).

These clinical indications may be a starting point from which each patient can find the optimal practice for his/her individual situation. The exact adjustments of insulin dose must be made only on an individual basis and these adjustments must be made learning by trial and error.

The trial-and-error approach works well because the intrasubject blood glucose responses to the same exercise's type, duration and intensity are reliable and repeatable when insulin regimens and preexercise meal are kept constant. Trial-and-error approach is an important finding for implementing and evaluating educational strategies to improve the metabolic control (51, 52).

"Doping" action of insulin therapy

There are evidences that some athletes take insulin to boost their performance illegally. It seems that about 10% of bodybuilders use insulin and that most of them obtained insulin from diabetic friends (53). Insulin illegally helps athletes in two ways: 1) insulin promotes muscle strengthening 2) insulin is a "ghost" drug because it is undetectable in the blood and when detected it is impossible to distinguish from athletes' own insulin (54). A good management of insulin doses together a correct eating behavior may determine a sort of legal "pseudo-doping" effect and this effect can be utilized in order to motivate people with T1DM to optimize metabolic control. The hypo- and hyperglycemic effects of exercise may cause discouragement and demotivation even in particularly gifted adolescents, which may lead to leave physical activity or to give up competitive sports (52)

Conclusion

Despite the difficulty in managing exercise, children and adolescents with T1DM appear to spend even more time in sport activity than their healthy peers. Diabetes does not seem to restrict children and adolescents with diabetes in their selection of sport disciplines in leisure time or in competition (3, 56). Physical activity has been known to improve risk factors for atherosclerosis, such as the lipoprotein profile, blood pressure, and to improve cardiovascular fitness. Furthermore, physical activity enhances the sense of well-being, self-esteem and quality of life in children and adolescents with diabetes (1, 5). However, studies have failed to show an independent effect of physical activity on improving glycemic control as measured by the A1C test in patients with T1DM (57). To enjoy physical activities without major metabolic complications, diabetic subjects have to acquire ability to modulate insulin therapy in prevision of and after exercise. Nonetheless, there are only few and not comprehensive recommendations. These guidelines often cannot be applied to daily insulin management but they may help to individualize insulin management for a single subject in a specific sport. This learning

"by trial and error" is widely suggested both by experts and by competitive T1DM athletes themselves. The ability to fully utilize the "trial and error" approach implies a full knowledge and application of the bases of therapeutic education, in particular insulin pharmacokinetic, blood glucose monitoring and interpretation, balanced feeding and physiology of exercise. To say it with Ulrike Thurm's words (52): "I feel that the characteristics that allow an athlete to compete successfully and also to maintain good blood glucose control are essential identical".

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