Insulin therapy and exercise

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ABSTRACT

Medical nutrition therapy and physical exercise are the cornerstones of the diabetes management. Patients with type 1 DM always need exogenous insulin administration, recently available in the form of insulin analogs. In type 2 DM, characterized by increased insulin resistance and progressive decline of the beta-cell function, various antidiabetic medications are used. Most of the subjects with type 2 DM will finally need insulin. The main site of insulin action is the skeletal muscle, while the liver is the main site of glucose storage in the form of glycogen. With the modern diabetes therapies it is possible to rapidly reach and maintain normoglycemia in both types of DM but with the cost of higher incidence of hypoglycemia, especially related to exercise. Regular physical exercise causes a lot of beneficial effects in healthy as well as diabetic subjects of all age groups. In type 1 DM physical exercise is a fundamental element for both physical and mental development. In type 2 DM it has a main role in diabetes control. The increased hepatic glucose production and the increased muscular glucose uptake during exercise are closely interrelated in all exercise intensities. In diabetes mellitus there is a disturbed energy substrate use during exercise leading to either hypo- or hyperglycemia. The influence of low or moderate intensity aerobic exercise on diabetes control has been well studied. The inappropriately high insulinemia combined with the low glucose levels can lead to severe hypoglycemia if proper measures are not taken. Prolonged exercise can also predispose to decreased glucose counter regulation. It is better for the type 1 diabetic subject to postpone the exercise session in very high (>300 mg/dl) or very low (<70 mg/dl) BG levels. Every insulin treated subject is recommended to be checked for any existing diabetic complication before the start of every exercise program. Glucose measurement with glucose meters or sometimes with Continuous Glucose Monitoring System (CGMS) must be made before, during and most importantly after the end of the exercise session. It is recommended either to reduce or suspend the previous insulin dose depending on the insulin regime or to receive extra carbohydrates before, during or after the exercise session or both. Subjects with type 1 DM may participate at almost all the competitive sports if precautions are taken. These measures must be individualized and readjusted, even empirically. In very high intensity exercise (about 80% of VO₂ max) or when high intensity exercise follows a low intensity one, there is a tendency of the BG to increase due to excessive circulating catecholamines necessitating postexercise short acting insulin. In anaerobic or resistance exercise lactic acid is produced. This exercise type is recommended for people in whom aerobic exercise is contraindicated. These two exercise types can be combined. The incidence of hypoglycemia or hyperglycemia in specific forms of resistance exercise as well as the appropriate insulin dose adjustment are not well studied. In conclusion all exercise types are beneficial for both types of diabetes.

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Medical nutrition therapy and physical exercise are the cornerstones of the diabetes management. The majority of patients with diabetes need also pharmaceutical therapy to manage the disease successfully. Patients with type 1 DM need exogenous insulin administration from the beginning of the disease to cover the basic and prandial insulin needs. In recent years, the introduction of insulin analogs helped these people take their insulin in a more "physiological" way. Type 2 DM is characterized by increased insulin resistance and a progressive decline of the beta-cell function. Various antidiabetic medications with different mechanisms of action are used, alone or in combination to treat type 2 DM. Most of the subjects with type 2 DM will finally need the administration of insulin in order to control their diabetes, either alone or in combination with oral antidiabetic agents [1]. The main site of insulin action is the skeletal muscle, where it increases the glucose uptake, while the liver is the main site of glucose storage in the form of glycogen after meals in the presence of insulin. Glucose is released by the liver between meals to maintain steady blood glucose levels (fasting plasma glucose in healthy subjects between 70 and 100 mg/dl). Insulin is secreted by the pancreatic beta cells after food intake and it increases glucose uptake in the muscle and fat cells, while it surpresses hepatic glucose production. In subjects with DM, both fasting and postprandial blood glucose levels are increased because of insulin insufficiency. With the new diabetes therapies, it is possible to rapidly reach and maintain normoglycemia in both types of DM, but at the cost of higher incidence of hypoglycemia, especially related to exercise. Drugs acting on the blood insulin levels (exogenous insulin and secretagogues) carry the higher risk for severe hypoglycemia related to exercise [1].

Regular physical exercise causes a lot of beneficial effects (physical and psychological) in healthy as well as diabetic subjects of all age groups. Especially in patients with DM, exercise improves all the parameters associated with the micro and macrovascular diabetes complications like body weight, blood pressure and lipids. In type 1 DM, physical exercise – either in the form of children’s play or sports – is considered to be a fundamental element for both physical and mental development, while its role in improved glycemic control is not yet clear [2]. There are however some recent works showing improved glycemic control and reduced body weight after exercise in children and adolescents with type 1 DM [3]. On the other hand, it is clear that in type 2 DM physical exercise has a main role in diabetes control [4].

In normal subjects during exercise, there is a fall in endogenous insulin production which compensates the increased glucose uptake by the exercised muscle. The increased glucose uptake is due to the recruitment of GLUT 4 transporters in the cell membrane. This effect of exercise in the muscle is mediated through an insulin-dependent and an insulin-independent way (through the muscular contraction). These two mechanisms act independently and synergistically in order to facilitate the muscle cell glucose uptake through the GLUT 4 transporters. There is also an induction of muscle hexokinase which phosphorylates glucose. The muscular glucose can either be stored in the form of glycogen or in aerobic conditions oxidized for energy production. There is also increased catecholamine and glucagon levels during exercise, which cause increased hepatic glucose production via increased glycogenolysis and neoglycogenesis, as well as increased triglycerides breakdown and free fatty acid (FFA) production from the fat cells. These FFAs can also serve as an energy substrate from the exercised muscle. The increased hepatic glucose production and the increased muscular glucose uptake during exercise are closely interrelated in all exercise intensities (Fig. 1). The exercised muscle can also use the stored glycogen and triglycerides as energy sources, mainly at the beginning of the exercise. The more intense the exercise, the more rapidly muscular glycogen is depleted. Muscular glucose cannot exit the muscle cell after its formation from glycogen breakdown, due to lack of the glucose-6-phosphatase, and so it cannot contribute to the blood glucose balance. At anaerobic conditions, anaerobic glycolysis is the main muscle energy source which leads to increased lactic acid production. For the exercise sessions to continue, it is often necessary to give exogenous carbohydrates at regular intervals during and after each exercise session to secure the appropriate energy sources and to replenish muscle glycogen stores [2].

In diabetes mellitus, where there is relative or absolute insulin insufficiency, there is a disturbed energy substrate use during exercise, also depending on the amount of the exogenous insulin, leading to either hypo- or hyperglycemia. There are many factors which may cause difficulties in glucose reg-

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The complete elucidation of the mechanisms of blood glucose disturbances during and after exercise in diabetes is very important for the successful outcome of various exercise programs in subjects with DM.

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ulation in exercised insulin treated subjects, during or even many hours after the end of exercise [2]. The influence of low or moderate intensity aerobic exercise on diabetes control has been better studied than this of other exercise types (Fig. 2). In this type of exercise glucose, glycogen and FFAs are used as energy substrates and hundreds of calories can be burnt. Examples are long distance, low to medium intensity running and marching, dancing, skiing, swimming and cycling. The main problems emerge from the fact that insulin levels cannot be appropriately suppressed during exercise in insulin treated diabetic subjects, as it happens in normal subjects, and from the fact that the hepatic glucose production cannot increase sufficiently to compensate for the increased glucose absorption by the exercised muscle, due to increased insulin sensitivity. There is also further increased insulin absorption and action at the site of insulin injection. The inappropriately high insulinemia combined with the low glucose levels can lead to severe hypoglycemia if proper measures are not taken [3,5]. Prolonged exercise can also predispose to decreased glucose counter-regulation because of decreased glucagon, epinephrine and cortisol levels during post-exercise hypoglycemia lasting several hours after the end of exercise, mainly during the night hours and mainly in type 1 diabetic subjects. It is also important that antecedent hypoglycemia can cause hypoglycemia unawareness and diminished counter-regulation during subsequent exercise [6]. It has been shown that women with type 1 DM can preserve better the counter-regulatory response in exercise after antecedent hypoglycemia than men [7]. On the other hand, if the insulin dose is largely reduced or a great amount of carbohydrates is taken, severe hyperglycemia or even ketosis may occur. It is better for the type 1 diabetic subject to postpone the exercise session if the BG level is above 250 mg/dl in the presence of ketosis or above 300 mg/dl in the absence of ketosis, until the metabolic abnormality is corrected.

Before starting on any exercise program, every insulin treated subject with type 1 or type 2 DM is recommended to be checked for any existing diabetic micro- or macrovascular complication. The existence of these complications will define the most suitable for each subject exercise program (type, duration and intensity). An exercise test on a treadmill is necessary when the diabetic subject is more than 35 years old, the diabetes duration is more than ten years in type 2 DM and more than 15 years in type 1 DM, there are cardiovascular risk factors, and there are either microvascular complications or peripheral vascular disease [8]. It is worth mentioning that there are appropriate exercise programs even for patients with severe diabetic complications, as severe diabetic autonomic neuropathy or hemodialysis-treated diabetic nephropathy. After the selection of the suitable exercise program, it must be emphasized that the duration and the intensity of every exercise session must be gradually increased. The diabetic subjects intending to exercise must be also properly prepared. As it is already mentioned, it is better to postpone or cancel the exercise session if the BG value is too low or too high. The glucose measurement with the glucose meters must be made before, during and most importantly shortly and many hours (sometimes more than ten) after the end of the exercise session. This procedure must be repeated many times until the effect of a specific exercise program on the blood glucose response becomes evident. If the program is modified, further measurements are needed. Sometimes, a continuous glucose monitoring with a CGMS device is necessary to clarify a glucose profile during and after an exercise program in order to prevent extreme glucose excursions especially in subjects with brittle diabetes. In order to avoid the blood glucose fall in hypoglycemic levels, it is recommended either to reduce the previous insulin dose or to receive extra easily absorbable carbohydrates before, during (30–60 g/exercise hour) or after the exercise session. The insulin dose reduction may even reach 90% [5]. It is obvious that insulin must not be injected in the exercised muscle groups. In the case of not programmed exercise, as it may often happen in children and adolescents, the only means to avoid hypoglycemia is the consumption of extra carbohydrates. If the subject bears an insulin pump, a reduction or even a stop of the basal insulin infusion, may be appropriate.

If the subject is in basal bolus therapy with fast acting insulin analogs, as is currently the case in most type 1 diabetic subjects, it is better to avoid exercise shortly after the injection of the analog. This regime allows great flexibility in
timing of the insulin injection and meals and snacks, as well as in the adjustment of insulin dose and bears the lesser risk for extreme glucose excursion during exercise compared with the older regimes. If human insulin is used instead as rapid acting insulin, exercise must be avoided three to four hours after the injection. If the exercise session is scheduled for these time periods, the previous fast acting insulin dose must be reduced, even if the exercise is of mild intensity (about 25% of VO\textsubscript{2max}). The more intense and longer the exercise program, the greater the insulin dose reduction. In the case of late afternoon or evening exercise, the following basal insulin dose must be also reduced, in order to avoid nocturnal hypoglycemia. Subjects with type 1 DM may participate in almost all the competitive sports, aiming even at Olympic medals, if the above mentioned precautions are taken. Special recommendations are given for each specific sport [5,9]. Many studies have shown that the hypoglycemia risk is reduced if a short bout of high intensity anaerobic exercise takes place at the end of the exercise session (e.g. 10 s maximal sprint) [10]. Hypoglycemia may also be avoided if the exercise session takes place early in the morning in the absence of both rapid acting insulin injection and breakfast. It must be remembered that, because of the greater morning blood concentrations of the counter-regulatory hormones, hypoglycemia is more frequent to occur during these hours. In this case the intake of extra carbohydrates may lead to hyperglycemia.

In case of insulin therapy with premixed insulin with certain amounts of long acting (human NPH, NPL or NPH aspart) and short acting (human regular, lyso pro or aspart) insulin, the so-called “split-mixed regime”, a 50% or greater preexercise dose reduction seems appropriate. It is already mentioned that subjects in pump therapy must reduce or even stop basal insulin administration rate during exercise. However, it is useful to restart insulin administration immediately after the end of the exercise, or even to give a small bolus dose in order to avoid postexercise hyperglycemia [11]. In young type 1 subjects who participate for many days in programs of increased physical activity (e.g. camps or championships), it is necessary to measure BG more often, to investigate the incidence of hypoglycemia or hyperglycemia. All these measurements must be individualized and readjusted, sometimes even empirically, so that the best results can be achieved [9].

In very high intensity exercise (about 80% of VO\textsubscript{2max}) there is a tendency for the BG to increase instead of dropping, compared with the medium intensity exercise (50% of VO\textsubscript{2max}) [12]. This is probably due to the excessive amount of circulating catecholamines, which lead to a more increased hepatic glucose production compared to the peripheral glucose uptake and a more profound endogenous insulin production suppression. This phenomenon may last until one hour after exercise. Many studies have shown that in type 1 diabetic subjects participating in very high intensity exercise programs like squash, cycling and running sprint, hypoglycemia is less frequent compared to exercise programs of less intensity. In type 2 insulin treated diabetic subjects hyperglycemia was more pronounced after high intensity exercise. It is often necessary to inject a rapid acting insulin bolus immediately postexercise, to lower BG levels. In repeated high intensity exercise programs, hyperglycemia becomes milder due to the individual’s adaptation to exercise (lower exercise catecholamine levels).

In exercise programs where low intensity exercise is followed by high intensity exercise of short duration, like children’s play or team sports (e.g. football), there is also a lower frequency of hypoglycemia (Fig. 3). These programs are suitable for young people (children and young adults) but not for older ones [10,13].

Besides aerobic exercise, there is the so called anaerobic or resistance exercise, where there is an isometric muscle contraction and the muscular strength is used e.g. to move a weight. In this type of exercise, lactic acid is produced and muscle glucose and glycogen are used as energy sources. This exercise type is recommended for people in whom aerobic exercise is contraindicated (e.g. in patients with severe diabetic neuropathy and cardiovascular complications). In some cases, the two exercise types can be combined. The resistance exercise increases the muscle mass and the bone mineral density, while it can improve the lipid parameters in type 2 diabetic subjects. There is also improvement in the overall glycemic control, as with the aerobic exercise [4,14]. However, there is a shortage of clinical studies which investigate the incidence of hypoglycemia or hyperglycemia in specific forms of resistance exercise as well as the appropriate insulin dose adjustment. This is strange given the facts that type 2 diabetic subjects comprise the large majority of the diabetic population and that physical exercise, in combination with nutrition therapy, is the cornerstone of the type 2 diabetes management. Evaluation of the effect of the various forms of resistance exercise like weight lifting and body building on the rate of either hypo- or hyperglycemia is also needed [8,14].
In conclusion, all exercise types are beneficial for subjects with both types of diabetes. Aerobic exercise must be carefully planned in patients with insulin treated diabetes in order to minimize the risk for either hypo- or hyperglycemia. The complete elucidation of the mechanisms that lead to blood glucose disturbances during and after exercise in diabetes is very important for the successive outcomes of various exercise programs in subjects with DM.

Conflict of interest

The author has no conflicts of interest to report.

REFERENCES