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Conference Report

Physical exercise and diabetes during childhood

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Abstract. Active life and physical fitness may represent the most effective strategies to prevent chronic diseases and to improve growth and development for children, including those with diabetes. Observational studies have demonstrated the association between life style and prevention of chronic diseases in the general population. These studies have been showed a reduction of morbidity for vascular diseases in trained subjects who present adequate cardiovascular fitness and practise regular exercise. The exercise-related protective effects may be mediated in part through components of the metabolic syndrome: improved insulin sensitivity, decreased weight and visceral fat accumulation, reduced low density lipoprotein (LDL) and triglycerides, increased high density lipoprotein (HDL), decreased blood pressure. These effects are more significant in patients with type 1 diabetes (T1DM), because hyperglycemia-related morbidity and mortality are associated with chronic complications. In particular, improved insulin sensitivity may determine a better glucose profile which in turn may positively influence the diabetes-related microvascular complications. Furthermore, improved blood pressure and normalization of lipid profile may also contribute to the prevention of vascular complications. Nonetheless, physical activity can improve psychological well-being by increasing self-esteem and enhancing quality of life. Although patients with T1DM may participate in all kind of sports and physical activities, there are several potential adverse events, including hypoglycemic and hyperglycemic episodes, that can occur. Thus, patients and health professionals have to know in details the physiological effect of physical exercise and its metabolic events in order sport to be healthy and enjoyable for all children, adolescents and young adults with T1DM. (www.actabiomedica.it)

Key words: Physical exercise, diabetes, childhood

Introduction

Regular physical activity has been represented a prime principles in the management of children and adolescents with type 1 Diabetes Mellitus (T1DM), even before the introduction of insulin therapy. Current guideline suggest the association of regular physical exercise, insulin therapy and adequate education as an essential component of the management of patients with T1DM (1). Nowadays, because all levels of physical activity can be performed by individuals with T1DM many patients are able to incorporate exercise into daily routine even as competitive performance (2).

Several studies have demonstrated the association between life style and prevention of chronic diseases in the general population (3). These observational studies have shown a reduction of morbidity for vascular diseases in trained subjects who present adequate cardiovascular fitness and practise regular exercise (4). The protective role of a higher exercise capacity is confirmed in the presence of different risk factors including diabetes. In fact all the several health benefits associated to regular physical activity for children are reported even in T1DM subjects. However, although patients with T1DM may be encourage to participate in all kind of sports and physical activities, several po-

tential adverse events could occur during physical exercise (1).

Thus physicians, children and young adults with T1DM may adequately know both the benefits and the risk related to muscle exercise in order sport to be healthy and enjoyable.

Exercise-related benefits and risks in children and young adults with T1DM

Physical exercise has been shown to have multiple health benefits for everyone including those with T1DM (table 1). In patients with adequate metabolic control, regular physical exercise improves insulin sensitivity leading to a significant daily insulin requirement (1). Furthermore regular activity appears to be associated to reduced glycaemic levels during and after muscle exercise and lower post-prandial glycaemic peak (5). Although these several benefits on glucose metabolism, controlled studies have not been able to show long-term improvement on metabolic control in patients with T1DM who practise regular exercise (6). However because optimized insulin therapy, meals and physical exercise are the three major factors influencing long-term metabolic control, these contrasting results may be in part explained. Exercise has others health-promoting benefits for people with and without diabetes. In fact numerous study have demonstrated that improvements in lipid profile and blood pressure occur with physical training (7-8). Physical training appears to improve muscle ability to up-take and oxidize free fatty acid. All these effects results in a protective role on the risk cardiovascular disease. Finally, all the beneficial effects on psychological well-being, cardiovascular fitness, muscle capacity and especially on obesity prevalence may be reported even for the patients with T1DM.

Although children and young adults with T1DM may be encourage to participate fully in sports, during physical exercise may occurs several potential adverse events (table 2) (9). The exercise-related influence on glucose metabolism and the subverted physiological modulation of insulin rate during and following exercise appear to be the first determinant in exercise-associated complications. In fact, in the setting of a fixed dose of insulin given prior to exercise, patients with T1DM may experience hypoglycemia both during and several hours following exercise. Hypoglycaemic episodes which can occur during exercise or 5-24 hours following exercise, may be due to hyperinsulinization, inadequate insulin/glucagon rate or increased insulin sensitivity. Furthermore physical exercise in patients with T1DM may be associated to an increased risk of both hyperglycemia and ketosis. In fact during physical exercise the occurrence of insulin repletion may induce increased blood glucose concentration mainly in patients with inadequate metabolic control. Moreover hyperglycaemia occurs even in patients who are well controlled and insulin-replete, during high-intensity exercise because increasing catecholamines and sympathetic nervous system dependent activation of hepatic glucose production which exceeds the rate of glucose utilization (10). Nonetheless physical exercise may worsen the diabetes-related chronic complications. Exercise negatively affects several early microvascular and macrovascular that may

Table 1. Benefits of physical exercise in patients with type 1 Diabetes Mellitus

- Reduces serum glycemic levels before and after exercise
- Improves insulin sensitivity
- Reduces of daily insulin dosage
- Improves post-prandial glycaemic peak
- Improves lipid profile
- Reduces weight and fat accumulation
- Improves cardiovascular facnction
- Improves blood pressare
- Contribution to psychological well-being and quality of life
- Improvement of muscle rate and capacity

Table 2. Adverse events during physical exercise in subjects with type 1 Diabetes Mellitus

- Hypoglycemia	
- Hyperglycemia	
- Ketosis	
- Worsening of microvascular complications	Retinopathy Nephropathy Neuropathy Autonomic Neuropathy

be detected in patients with T1DM mainly in those patients with long diabetes duration. In fact, in patients with retinopathy, vigorous exercise produces significant increases in blood pressure and can accelerate proliferative diabetic retinopathy with risk of retinal and vitreal haemorrhage and detachment. Although no controlled trials have been demonstrated the association between exercise and progression of diabetic nephropathy, vigorous physical exercise is associated to an increased amount of protein excreted in the urine in patients with proteinuria (11-12). However as exercise also help to reduce blood pressure chronically the resulting benefits are not clear cut and at present no guidelines exist on either the benefits or risks of exercise in the presence of nephropathy. In patients with diabetic nephropathy, the underlying lack can predict unnoticed foot ulcers and may induce articular and tissue injury. Because the autonomic nervous system is involved in all involuntary regulations, diabetic neuropathy can produce a wide variety of effects as decrease maximal cardiac capacity and outputs, decreased cardiovascular rate to physical exercise, orthostatic hypotension, impaired sweating, impaired gastrointestinal function that may be exacerbate during exercise (13-16). Furthermore exercise may precipitates episodes of angina in adults with diabetes with an increasing risk of underlying cardiac disease (17).

All these effects let to well understand both the prominent importance of regular physical and the potential adverse events related to exercise in patients with T1DM. Thus it is of foremost importance that physicians and children and young adults with T1DM well known all the hormonal and metabolic changes that occur during muscle exercise in order to prevent adverse events during physical exercise.

Metabolic and glycaemic changes during exercise

Tissue and circulating energy content provided by the three major fuels: fats, carbohydrates and proteins. These different energy sources may be divided into storage sources which may be mobilized after increased request, and circulating sources which are immediately available. The energy sources provide different energy. However, although fat caloric support is higher, carbohydrate and especially muscle and liver glycogen represent the most important caloric font directly modulating control of glucose metabolism (18).

At rest blood glucose concentrations must be maintained within narrow limits. In this state, roughly half of glucose uptake occurs in the brain, while only 20% is taken up by the muscle (18).

In the post-prandial state increased blood glucose causes a rise in insulin release which reduces hepatic glucose production and increases the disposal of glucose in peripheral tissue. Some 90% of this clearance occurs through increased uptake in skeletal muscle mediated by GLUT-4 (19). In fact it has been widely demonstrated that insulin receptor activation induces the translocation of the transporter protein to the membrane surface (20).

During exercise there is an increase in blood flow to the working muscles to improve oxygen delivery, carbon dioxide disposal and energy substrate. Furthermore, because increased muscle energy requirements, blood glucose concentration falls leading to suppression of insulin secretion and to activation of a variety of counter-regulatory response (21). Elevation in blood concentration of hormones like epinephrine, norepinephrine, glucagons and growth hormone promote activation of hepatic gluconeogenesis and glycogenolysis, adipose lipolysis hepatic and muscle glycogenolysis. Furthermore exercise induces an increased muscle glucose up-take through the insulin-independent GLUT transporter recruitment (22). In fact it is well know that exercise modulates GLUT translocation through different pathways inducing glucose increased uptake and utilization. As the same effects have been demonstrated even by glycogen depletion, progressive glycogen utilization occurring during exercise determine increased GLUT-dependent glucose up-take in the post-exercise state (22).

The metabolic and hormonal changes during exercise are sequentially characteristic for each different phase of exercise (figure 1) (23-24). At rest the skeletal muscle energy sources are mainly fats and the hormonal control results from a balance between insulin and glucagon secretion. Requirement of exercising muscle is first supplied by intracellular depot of adenosine triphosphate for the first minutes while the following minutes of muscular work are maintained by

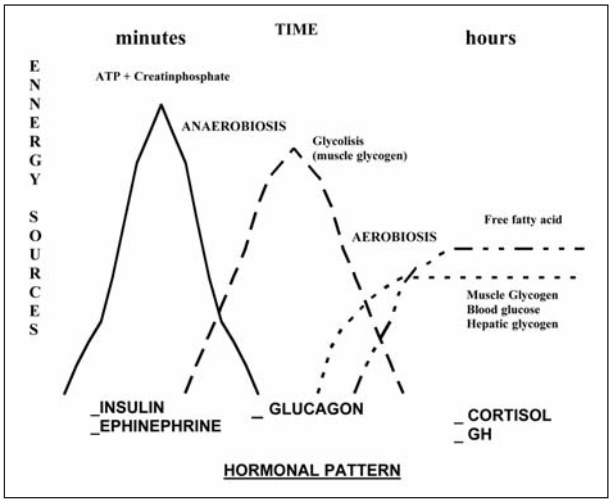

Figure 1. Integrated model metabolic and hormonal changes during exercise are sequentially characteristic for each different phase of exercise

muscle glycogen and by blood glucose. These two first phases are characterized by decreased absolute insulin levels and increased epinephrine levels and local relative insulin levels related to the increased blood flow to the working muscle. As exercise belong muscle metabolizes blood glucose and successively during prolong exercise blood glucose and fatty acids. During prolonged exercise hormonal response results respectively in increased secretion of cortisol and growth hormone (22-24).

Factors affecting metabolic changes during exercise

During physical exercise the energy request progressively increases in the working muscle. However the energy sources differ according to different factors. In fact, several factors have been recognized to affect the way that the body metabolizes fuel in the setting of exercise: duration of exercise, intensity of exercise, physical training and preexercise diet (25-29).

Duration of exercise represent an important factor that have been demonstrated to modulate fuel metabolism during exercise. Over time metabolism shifts from mainly glucose oxidation to fatty acid oxidation. In fact during shorter physical exercise glycogen and blood dependent glucose is greater than fat in the working muscle; while during longer exercise fat becomes the predominant fuel (26).

Intensity of exercise expressed by *VO2max* also affects fuel metabolism. During high intensive physical exercise almost all of the metabolic fuel source is glucose. However during low intensity exercise fat utilization increases and glucose oxidation drastically decrease (27).

Physical training may also have an important impact on fuel metabolism. In fact training improves the ability to use fat for energy, insulin sensitivity and skeletal muscle glycogen synthase activity. Thus individuals who are trained athletes utilize fuel more efficiently and lipid better than untrained subjects (29).

Finally pre-exercise diet can affect fuel metabolism during exercise (28). In fact, increased carbohydrates oxidation during exercise may be secondary to a diet rich in carbohydrates. Furthermore carbohydrates intake may also restore hepatic and glycogen store prior to exercise leading to adequate glucose production during the following exercise.

Metabolic and glycaemic changes during exercise in patients with T1DM

Correct knowledge on the metabolic and hormonal response to physical exercise let to well understand the biochemical disturbance that may occur during muscle exercise in patients with diabetes. In fact during exercise even in patients with T1DM there is an increase in blood flow to the working muscle groups to improve oxygen delivery, carbon dioxide disposal and energy substrate. Furthermore, because increased muscle energy requirements, blood glucose concentration falls. However the regulation of blood glucose concentration during exercise is not as well-controlled as it is in normal subjects. In fact the physiological suppressed insulin levels may not be physiologically regulated leading to higher or lower insulin levels. All these alterations result in a inadequate or exaggerated glucose muscle uptake, inadequate or exaggerated glucose liver production, inadequate or exaggerated free fatty acid production in adipose tissue. Because the blunted metabolic changes, exercise in patients with T1DM may induce hypoglycaemic or hyperglycaemic episodes which could onset both during and several

hours following exercise.

Exercise-dependent hypoglycemia in patients with T1DM

The exercise-dependent fall in blood glucose concentration observed in diabetic subjects represent the most frequent adverse event during muscle activation (30). During and following muscle work in patients with T1DM, several circumstances may induce an absolute increased blood insulin concentration which results in hypoglycaemia. First, because type 1 diabetes related insulin absolute deficiency, muscle exercise onset does not permit adrenergic dependent insulin suppression (31). Furthermore because insulin is delivered by injection or pump, serum insulin concentration are independent by exercise and moreover may be enhanced by exercise if injected in exercising area (32). As detected in normal subjects, even in patients with T1DM exercise induce increase insulin sensitivity that may induce exaggerated glucose uptake. This effect appears to be enhanced by hyperinsulinemic levels and especially after exercise cessation. In fact following exercise, because the increased insulin sensitivity and the depleted glycogen stores, muscle glucose uptake increases leading increased insurgence of hypoglycaemia most commonly nocturnal (33). In addition because insulin levels may not be suppressed during exercise, the elevated insulin levels may be associated to blunted insulin/glucagons rate and inadequate hepatic glucose production (34). Moreover counter-regulatory response appears to be blunted in patients with diabetes. In fact in patients with T1DM decreased sympathetic nervous system response have been detected. These alteration result in decreased counter-regulatory responses to exercise related falling glucose levels (35). All these factors determine the increase the risk of exercise-induced hypoglycaemia in patients with T1DM.

Several factors may affect the abnormal neurohormonal changes detected during exercise in diabetic patients enhancing the occurrence hypoglycaemia: glycaemic trend, antecedent hypoglycemic episodes, timing of exercise according to the last insulin injection, enhanced absorption of peripherally injected insulin, duration and type of sport, enhanced insulin sensitivity after exercise, timing and composition of pre-exercise diet, autonomic defects (table 3) (36-39). The glycaemic trend before, during and after exercise and especially antecedent hypoglycemic episodes represent an important factor affecting a significant fall in blood glucose concentration. In fact antecedent hypoglycaemia blunts the neuro-hormonal changes during exercise inducing an increased risk of hypoglycaemia during the subsequent muscle activation (36). The same effects have been reported in subject who have performed prior exercise (37).

Table 3. Risk factors influencing the occurrence of hypoglycemic episodes during sport

- Glycemic trend
- Timing of exercise according to the last insulin injection
- Enhanced absorption of peripherally injected insulin
- Duration and type of sport
- Enhanced insulin sensitivity after exercise
- Timing and composition of pre-exercise diet
- Antecedent exercise
- Autonomic defects

The timing of exercise according to the last insulin injection also represents an important factor affecting the occurrence of hypoglycaemia during sport. In fact because enhanced absorption of peripherally injected insulin, hypoglycaemia risk is higher as shorter is the time of the last insulin injection from the exercise onset. This effect may be enhanced by insulin injection into working muscle (39).

Thus several factors may influence the occurrence of hypoglycemic episodes during sport. Physician and subjects with diabetes mast well known all these variables in order to prevent acute and late hypoglycaemia.

Exercise-dependent hyperglycemia in patients with T1DM

During muscle exercise, the physiologically suppressed insulin concentrations represent the first response of the body in order to prevent hypoglycaemia. However adequate insulin concentrations regulate blood glucose levels and prevent hyperglycemia. Furthermore insulin facilitates glucose uptake locally

Table 4. Risk factors influencing the occurrence of hyperglycemic episodes during sport

- Glycaemic trend
- Timing of exercise according to the last insulin injection
- Duration and type of sport
- Hydration State

in the working muscle and may balance an excessive blood glucose increased due to counter-regulatory hormones. Thus, severe hyperglycemia and ketoacidosis could develop if both insulin levels are too low before exercise and if muscle activity starts at insulin levels that are too low to induce these regulatory effects (40). As exercise begins, hyperglycemia and ketoacidosis will deteriorate, with a further increase in the production of counter-regulatory hormones which induce hepatic glucose production and impaired muscle glucose up-take and as a result rises in blood glucose (41). During exercise the hyperglycaemic and ketosis occurrence may be influence by several risk factors (table 4). Timing of physical exercise according to the last insulin injection may strongly influence hyperglycemia and ketosis. In fact because insulin concentrations decrease progressively after injection, exercise-related hyeprglycemia may be detected if exercise starts too late according to the last insulin injection. All these effects may be enhanced if poor metabolic control defined by higher glycaemic trend occur before exercise (42). The risk of hyperglycemia is increased by prolonged and high intensity exercise (43). In fact during prolonged muscle lipid utilization increase instead of glucose. Furthermore during high intensity exercise [VO2 max > 80%] the conter-regulatory response induce a drastic and rapid increase in glucose production. Adequate hydration may influence hyperglycemia in the setting of physical exercise. In fact as dehydration induces a relative hyperglycemia during sport, adequate water load must be take before and during sport.

Strategies to prevent exercise induced adverse events in patients with T1DM

Adequate knowledge of the several changes and modulating-factors occurring during and following a period of physical exercise in T1DM represents an important advice on prevention of complications.

Diabetes education should focus on individualize strategies to each patient based on their specific response to a particular activity. Insulin demands during exercise might differ substantially and first of all individual experience must be collected in order to minimize risk and thus glycemic control may be individually optimized.

Although the importance of individual response to physical activity is know well recognized, basilar advice may be taken into account. If physical exercise is programmed prefer to start exercise roughly 1-3 hours after a meal and insulin administration. Furthermore manipulation of the daily insulin dosage and site of injection may be useful approach to prevent hypoglycaemia. In fact adequately relative-low insulin levels by reducing dosage prior exercise and by avoiding working area may reduce the rapidly increased glucose up-take.

Careful check of blood glucose levels is also important to prevent hyperglycemia and ketosis during and after exercise. In fact low insulin levels induce increased blood glucose which if documented prior exercise may be enhanced by muscle working especially by high intensive exercise. Thus supplemental insulin should be given and exercise can begin once glucose levels have fallen and ketosis has resolved.

Prior exercise diet need adequate carbohydrates intake as blood glucose represent the most important energy sources. Because muscle glucose uptake is increasing during exercise, patients with diabetes have to check blood glucose before and during muscle working. If low levels are documented consider taking carbohydrates prior or during activity. Furthermore additional carbohydrates intake are needed if exercise is longer than 30 minutes in order to prevent late onset hypoglycaemia. However whether it is usually required or not, the child and her family should have fasting glucose available for emergency use during and following period of exercise.

For children who are involved in activities it is important to let coaches or supervising adults know of possible exercise related adverse events and have fasting glucose and glucagons available for emer-

gency.

All subjects with T1DM may undergo a detailed medical evaluation on the symptom and signs of manifested disease of heart and blood vessels, eyes, kidneys feet and nervous system. The screening of microvascular and macrovacsular complications may consent adequate advise in order to practise a safe sport.

Conclusion

Current recommendation for children and adolescents with T1DM encourage physical activity. While several adverse events may occur during physical exercise in patients with diabetes, T1DM subjects may be encourage to practise sport that may be aerobic, moderate intensity, medium-long duration, regular, programmed (as possible), self-monitored, adequately hydrated and fuel integrated.

Patients and health professionals have to know in details the physiological effect of physical exercise and its metabolic events in order sport to be healthy and enjoyable for all children, adolescents and young adults with T1DM. Association of regular physical exercise, insulin therapy and adequate education represent an essential component of the management of patients with T1DM.

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