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INTENSİVE PHYSİCAL EXERCİSE AND KETOSİS İN TYPE 1 DİABETES: LİTERATURE REVİEW ON A CASE AFTER COVİD-19 QUARANTİNE

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ABSTRACT

Type 1 diabetes (TD1) is characterized with elevated blood glucose due to insulin deficiency. In case of insulin deficiency glucose can not be used by the body cells to generate energy. Therefore, triglycerides (TG) and free fatty acids (FFA) become source of energy. Ketone bodies (KBs) are synthesized through beta oxydation of FFAs in the liver. KBs serves as an alternative source of energy. The ability of muscle cells to use KBs in energy production is dependent the insulin. Insulin deficiency in individuals with T1D causes both the increased synthesis of KBs and also inability to use the KBs as source of energy. Accumulation of KBs in the blood is known as hyperketonemia (ketosis). Elevated KBs cause a decrease in blood pH, thereby, a diabetic complication diabetic ketoacidosis develops. On the other hand ketosis in individuals with T1D can develop due to insulin deficiency and prolonged hyperglycemia, as well as prolonged fasting state or prolonged and intensive physical exercises. In this study, we present hyperketonemia situation in a child with T1D that was atributed to the intensive physical exercises in and reviewed the relevant literature data.

Key Words: Type 1 diabetes, Exercise, Ketosis

INTRODUCTION

T1D is a chronic disease that usually occurs in childhood. The treatment of the disease is provided by insulin, appropriate nutrition and controlled physical exercises. This disease must be well managed to reduce the risk of acute and chronic complications.[1-6] The most important issue for good management of T1D is to maintain the balance between insulin and carbohydrate (CHO). Disruption of this balance can cause serious problems for individuals with T1D. Hypoglycemia is the most serious acute complication in individuals with T1D. Many situations such as skipping meals, intense physical activity, using too much insulin can cause the development of hypoglycemia. [1] Hyperglycemia may occur due to eating too much, not making enough insulin, skipping insulin doses or infectious diseases.[9] If glucose can not be taken into cells due to insulin deficiency, glucose oxidation will decrease dramatically. In this case, cells will use fats for their energy needs. In this process, the amount of FFAs passing from adipose tissue into the blood increases. The synthesis of KBs (acetone, acetoacetate, β-hydroxybutyrate) also increases as a result of metabolism from FFAs in the liver. Normally synthesized KBs are sent to tissues other than the liver and used for the energy needs of the tissues.[18] Due to insulin deficiency in individuals with T1D, the production of KBs increases and these bodies cannot be used as energy in tissues. Thus, KBs accumulate in the blood and cause the development of a condition called ketosis. Uncontrolled ketosis causes ketoacidosis, which is a serious acute complication. Ketosis usually occurs with a prolonged high blood glucose level. However, due to intense physical exercises and skipping meals, individuals with T1D can develop ketosis without hyperglycemia. Especially in some children with T1D, this situation occurs with symptoms such as abdominal pain, nausea and vomiting. There is no doubt that there are children with T1D who usually have breakfast late in the summer. These children can skip lunch and finish the day with dinner. It is thought that long-term intense physical exercise in hot weather may increase the risk of ketosis. In addition, CHO and insulin deficiency caused by skipping meals further increase the risk of ketosis. In this study, the effect of intensive physical exercises and skipping meals on the development of ketosis was evaluated within the framework of the T1D child case and the literature.

MATERIALS AND METHODS

The study was conducted by examining the data of the child case with T1D within the framework of the literature. The data of the case were obtained from the interview with the parents of the case. In accordance with the Helsinki Declaration, a consent form was prepared and signed by the case and his parents.

Subjects

The case is a boy aged 9 years old and has T1D for 6 years. The height of the case is 128 cm and his body weight is 29 kg. The case uses fast acting (insulin lispro) for bolus and long acting insulin analogs (insulin glargine) for basal. The case makes CHO count as a nutritional method. Accordingly, 10 grams of CHO at breakfast, 15 g of CHO at lunch, 1 unit of fast acting insulin for 20 g CHO at dinner is used. In the evening, 8 units of long-acting insulin injections are applied. The insulin sensitivity factor (ISF) of the case is 100 mg / dL for 1 unit of fast acting insulin. The regulation factor (RF) for hyperglycemia was calculated as 1 unit of fast acting insulin per 100 mg / dL above 150 mg / dL. The patient uses the accuchek glucose meter for blood glucose control and measures blood glucose at least 8 times a day. He uses the FreeStyle Libre device to measure the ketone level in the blood.

The data of a day when the subject played children's games for 7 hours is presented in Table 1. These games include exercises with different load intensity. These data were recorded by the parent of the T1D case. Table 1; It includes fasting and postprandial blood glucose levels, the amount of CHO consumed in main and snack meals, bolus and basal insulin doses, ketone levels, activities performed during the day and some symptoms

Table 1.Measurements and some determinations made by parents at home.

First Day	Hour	Fasting Glucose mg/dL	Main Meal CHO(g)	Fast-acting Insulin Dose	Postprandial Glucose mg/dL	Long-acting Insulin Dose	Snack CHO(g)	Ketone mmol/L	Events and Situations
Morning	10.00	136	25	2.5	158	-	10	-	Rest at home until 11:50
Noon	15.00	130	-	-	-	-	-	-	He played a game with physical exercise between 12.00-19.00 in the residential garden. He did not eat lunch.
Evening	20.00	105	70	2	159	8	-	-	He rested and slept at 22:00.
Night	03.00	340	-	1,5*	-	-	-	-	He woke up with stomach ache, nausea, and vomited.
	06.00	140	-	-	-	-	-	-	
Second Day									
Morning	09.00	198	20	1,5	158	-	-	**0,7**	Abdominal Pain and Nausea
Noon	13.00	178	10	-	60	-	20	-	Abdominal Pain and Nausea
Evening	18.00	170	30	1,5	150	8	-	-	Abdominal Pain, Nausea and Vomiting
Night	00.00	129	-	-	-	-	-	**1,1**	Abdominal Pain, Nausea and Vomiting

* Additional insulin dose for regulation

As the vomiting continued on the night of the second day, as shown in Table 1, the emergency of the hospital was visited. Laboratory results and evaluation are presented in Table 2.

Table 2. Laboratory results and evaluation

Second Day	Hour: 01.30	Clinical evaluation and recommendations
Blood Glucose (mg/dL)	122	Ketone was found to be high in urine. The patient's abdominal pain continued to be mild, and the examination was normal. There was no nausea and vomiting. It was recommended that the insulin regimen be continued, the patient should rest and drink plenty of fluids.
Ketone in urine (mg/dL)	10	
Ph	7,390	
pO_2 (mmHg)	36,5	
Sodium (mEq/L)	136	
Potassium (mEq/L)	3,7	
CRP (mg/L)	4,2	

Type 1 Diabetes and Hyperketonemia

Glycogenolysis, gluconeogenesis, lipolysis and ketogenesis are chemical processes which are carried by activation of anti-hormone insulin. The occurrence of these processes depends on whether there is sufficient insulin in the concentration. T1D is a chronic metabolic disease that develops due to insufficiency or deficiency in the secretion of insulin hormone. It is stated that many factors are effective in the development of this disease .[3] T1D mostly (90%) develops by autoimmune destruction of the beta cells of the pancreas. [3-16-17] Insulin is an anabolic hormone that provides glucose, protein and fat storage in the tissues. Storage of glucose in fat and muscle tissue with insulin deficiency causes a number of problems. The renal glucose threshold is exceeded when the plasma glucose concentration rises above 180 mg / dL. As a result, glucosuria, polyuria, electrolyte losses and dehydration develop. In some cases that cause stress in individuals with T1D, there is an increase in anti-insulin hormones. The increase in epinephrine (adrenaline), glucagon, growth hormone and cortisol stimulates glycogenolysis, gluconeogenesis, lipolysis and ketogenesis by antagonizing the effect of insulin .[32] Cortisol, growth hormone, glucagon and adrenaline increase glucose production in the liver. Adrenaline activates four chemical processes. Glucagon, which activates the gluconeogenesis and ketogenesis. While cortisol activates gluconeogenesis, growth hormone activates lipolysis .[4-24] FFAs released as a result of increased lipolysis turn into acetylcoenzyme A (acetyl-CoA) in the liver. The increasing acetyl-CoA's cannot be fully oxidized and turn into KBs (acetone, acetoacetate, β hydroxybutyrate). In insulin deficiency, KBs are not used in energy production.Glycogen in skeletal muscle cells is the primary source of energy required for muscle contraction. Glycogenolysis occurs with the depletion of muscle glycogen stores and a decrease in blood glucose level. Thus, blood sugar is prevented from falling. During long hunger and intense physical exercises, the decrease in blood glucose is basically prevented by the release of hormones such as glucagon and adrenaline. Especially in long-lasting exercises, skeletal muscles meet their energy needs from TG and FFA. This process is not a problem for healthy individuals, but it may cause some health problems in individuals with T1D. These chemical processes are affected by the insulin dose and the amount of CHO in individuals with T1D. If the balance between CHO and insulin is not established, hypoglycemia or hyperglycemia may develop. In both cases, it carries serious risks. During the hyperglycemia that develops due to the inability of glucose into the cell, the cells obtain their energy need from TG and FFAs. Hormonal responses secondary to insulin insufficiency and intracellular glucose deficiency increase the formation of KBs (acetoacetate,-hydroxybutyrate, acetone) from FFAs in the liver. Blood KBs level in normal individuals is >0.5mM. However, in case of long hunger, this level can rise up to 6–7.5 mM. [13-25] It is stated that KBs increase up to 25mM in individuals with uncontrolled T1D. [11] Individuals with T1D should replace muscle glycogen to reduce the risk of complications during and after physical exercises.[8-23] It is very important for these individuals to follow insulin regimens without skipping meals in terms of replenishing muscle glycogen stores. Insufficiency in glycogen stores increases the production of KBs and causes these bodies to accumulate excessively in the blood. In this way, blood pH is disrupted and a complication considered as ketoacidosis develops .[17-32]

Type 1 Diabetes and Exercise

Physical activity is all bodily movements that require energy expenditure above the basal level .[26] Exercise is repetitive body movements that are performed in a planned way to improve or maintain physical fitness. [7] Regular physical exercise has many positive physiological effects for individuals with T1D. In addition, it is also very important in terms of psychosocial .[2-17-26-30]

Regular exercise, as well as insulin and diet, is an important part of the treatment process to ensure glycemic control in T1D. [17-22] Skeletal muscles are responsible for approximately 80% of glucose use and are highly determinant in the regulation of blood glucose. [7] Regular exercise improves strength, cardiovascular endurance, flexibility, and body composition, which are health-related parameters of physical fitness. It is also recommended for providing psychosocial fitness and delaying macrovascular complications. [17-26] It is stated that it is important to include aerobic exercises in the physical exercise programs of individuals with T1D. [2] Aerobic activities include moderate exercises such as walking, jogging, cycling, swimming where 40-60% of VO_{2max} or 50-70% of HR_{max}. [14-20] Anaerobic exercise is a workload above the anaerobic threshold. These

exercises increase the muscle and blood lactic acid levels and create fatigue in a short time. [31] The intensity of these exercises is expressed as 80% and above of VO_{2max} or 75% and above of HR_{max} .[14-35] 70-85% of HR_{max} is defined as mixed zone and 85% above of HR_{max} is defined as anaerobic zone for young people. [20-21] Resistance exercises are an exercise method against resistance to improve strength parameters such as maximal strength, rapid strength and continuity in strength. .[15] Hormonal and metabolic responses created by resistance exercises are similar to anaerobic exercises. [29-35] It can be said that both aerobic and anaerobic metabolisms are effective in many games played by children and adolescents. These games, which include physical exercises, do not pose any risk for normal children. However, it carries serious risks for children with T1D, such as hypoglycemia, hyperglycemia, and hyperkatonia. Hyperglycemia and excessive ketosis during exercise are particularly undesirable since they cause dehydration and may decrease blood pH, both of which impair exercise performance. Anaerobic exercises may particularly aggravate this condition, since increases in catecholamines and glucocorticoids will further exaggerate the elevations in blood glucose concentrations and ketone production.[21-29]

DISCUSSION

Muscle glycogen is the primary fuel source during moderate and high intensity exercise. Muscle glycogen is largely depleted in the first half hour of exercise. When the glycogen stores decrease in body, other fuel sources are used. In addition, glucose, which is added to the circulation from hepatic glycogenolysis and gluconeogenesis, is important for balancing blood glucose and providing energy. With the dramatic decrease in muscle glycogen and blood glucose levels, muscle TGs and circulating FFAs produced by hormone sensitive lipase act as a fuel source. Beta oxidation of fatty acids occurs in the liver. Thus, the productivity of KBs also increases. KBs are characterized as fasting ketones, unlike ketosis that develops during hyperglycemia due to insulin deficiency. [3] Ketogenesis is a chemical process that normally occurs under fasting conditions. KBs play a role in energy production under conditions where glucose is limited. Gluconeogenesis, lipolysis and ketogenesis increase with the effect of insulin deficiency and opposite regulatory hormones in individuals with T1D .[34] The curfew imposed in the Covid 19 pandemic is very boring for all children. The case played in the residence garden for a long time in a day in the summer when the quarantine was relaxed. It was stated by her parents that the case played games with his friends for 6-7 hours and that these games such as football, catching, hide-and-seek, and cycling involved intense physical effort. During this time, he came home only once and measured his blood glucose level. Blood glucose level was determined as 130 mg / dL by his parents. The case did not want to eat lunch, only drank water and returned to the garden to play. It is clear that the case who did not skip meals before did not want to enter the house due to the boredom of the quarantine application. Especially in the covid-19 quarantine, the need for all children to play has increased. For this reason, it can be said that the case stayed on the street for a long time. It is seen that the blood glucose level of the case is not risky in terms of hyperketonomia. The good blood glucose course of the case may be associated with the effect of basal insulin. It is a known fact that glycogen is insufficient for the increased energy need with long-lasting intense physical exercises. In this process, due to the CHO deficiency caused by the case skipping meals, it accelerated the use of alternative sources for energy needs. Thus, it increased the amount of FFAs in circulation. In parallel with this, ketogenesis was activated and more KBs were produced than normal. Hyperketonomia that develops during and after prolonged hunger and physical exercise can cause symptoms such as abdominal pain, nausea and vomiting, especially in children with some sensitive T1D. In the study conducted by Albada and Waarde (2016), ketosis was detected in a patient with T1D at night of the exercise day. In the study, it was reported that the patient experienced nausea on these nights. Frry et al. (1987) emphasized that the hyperketonemic effect of prolonged exercise in T1D was not due to exaggerated stimulation of ketogenesis. In the study, it was stated that the probable cause of this situation was insulin deficiency.

CHO consumption is the main factor for glycogen synthesis. About a quarter of the consumed CHO's are stored in the liver in the form of glycogen. Hepatic glycogen storage peaks 4 to 5 hours after eating. More CHO is needed to replace muscle glycogen (Radziuk and Pye, 2001). In this respect, CHO consumption at meals is very important for individuals with T1D. Insulin dose should be adjusted according to the CHO rate consumed and the duration and intensity of exercise. This arrangement is very important in terms of preventing hypoglycemia caused by exercise as well as preventing hyperketonemia.

Conclusion and Recommendations

In healthy individuals, KBs are released into the blood after they are produced in the liver. Among these bodies, acetoacetate and β hydroxybutyrate are used as energy in the surrounding tissues outside the liver. It is known that insulin has an accelerating effect on the use of KBs as energy. KBs effectively cannot be used for energy production due to insulin insufficiency in individuals with T1D. As a result, acetoacetate and β-hydroxybutyrate except acetone accumulate in the blood. KBs that exceed a certain level in the blood can

cause conditions such as abdominal pain and nausea.Replenishing muscle glycogen after long and intense exercise is very important for health and exercise performance. In other words, hepatic glycogen must be recovered to prevent hyperketonomia that may occur after exercise. Depletion of glycogen stores during intense exercises in individuals and athletes with T1D may cause excessive synthesis of KBs. High KB levels due to prolonged physical activity and fasting were seen in the case. Therefore, it is very important to renew glycogen stores for physically active individuals with T1D. Especially children with T1D should not neglect their meals and insulin infection. This issue should be considered by both diabetic children and their parents. It should be kept in mind that the risk of ketosis is high, especially in the hot summer months. At these times, children with T1D should be careful in games that require physical effort and take necessary precautions, which will reduce the risk of complications. As a result, adjustments should be made in the meals and insulin doses of all individuals with T1D according to the duration and intensity of their physical activities. Recommendations of health professionals and past practices should be used for these regulations.

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