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Cambios en parámetros metabólicos e inflamatorios en un paciente diabético tipo 1 realizando actividades extremas

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ABSTRACT

Background: physical activity in type 1 diabetic patients allows a better control of glycaemia and glycosylated hemoglobin, helps to maintain a residual endocrine pancreatic mass and optimizes subsequent insulin requirements. These improvements might be due in part to increases in anti-inflammatory cytokines that could help to minimize β-cell destruction. However, type, intensity and frequency of exercise for type 1 diabetic patients remain to be established.

Case report: we present the case of a 48-year-old man diagnosed with type 1 diabetes at the age of 23. He is a professional alpinist and recently was recruited in a program of the Yuri Gagarin Cosmonaut Training Center (Russia) to be the first diabetic astronaut. Metabolic and inflammatory responses were assessed after performing two extreme activities.

Discussion: well programmed extreme activities accompanied by a correct dietetic intervention can reduce the adverse metabolic and inflammatory processes that appear due to exercise and diabetes.

Key words: Cytokines. Diabetic alpinist. Diabetic astronaut. Extreme situation. Stress.

RESUMEN

Introducción: la actividad física en pacientes diabéticos tipo 1 permite un mejor control de la glucemia y hemoglobina glucosilada, ayuda a mantener una masa residual de páncreas endocrino y optimiza las necesidades de insulina. Estas mejoras podrían ser debidas en parte al incremento en citocinas antiinflamatorias que ayudarían a minimizar la destrucción de células β. Sin embargo, el tipo, la intensidad y la frecuencia de ejercicio para pacientes diabéticos tipo 1 no han sido establecidos.

Caso clínico: presentamos el caso de un varón de 48 años de edad diagnosticado de diabetes tipo 1 a los 23. Es alpinista profesional y recientemente ha sido reclutado por el Centro de Entrenamiento para

Cosmonautas Yuri Gagarin (Rusia) para ser el primer astronauta diabético. Hemos comparado respuestas metabólicas e inflamatorias tras realizar dos actividades extremas.

Discusión: actividades extremas bien programadas y con una correcta intervención dietética pueden reducir la descompensación metabólica e inflamatoria causada por la combinación actividad-enfermedad.

Palabras clave: Citocinas. Alpinista diabético. Astronauta diabético. Situación extrema. Estrés.

INTRODUCTION

It is well known that physical activity has beneficial effects on an individual's overall health. In this respect, physical exercise as part of their regular habits in individuals with type 1 diabetes has the potential to help them manage their disease more efficiently (1). Type 1 diabetes is an autoimmune disease in which pancreatic β-cells are destroyed, forcing the patients to inject themselves insulin for the rest of their lives (2). Very often, patients diagnosed with type 1 diabetes tend to be less physically active than healthy people. Fear to disease, management of glycaemia and risk to suffer hypoglycemic episodes are the main obstacles that type 1 diabetic patients must face when performing physical activity (3). This situation of inactivity favors the development of cardiovascular disease, overweight and joint pain, as well as the early appearance of diabetic complications (1,3). Fortunately, recent new technological advances allow patients to continuously monitor their glucose levels and optimize insulin intake, allowing diabetic patients to better manage their disease and perform with no risk physical activity (4).

Active type 1 diabetic patients present a decrease in glycosylated hemoglobin, post-exercise and post-prandial glycaemia, resulting in a reduction of injected insulin (5). Since the development of microvascular complications (i.e., retinopathy and nephropathy) are strongly related to glycemic control, exercise might delay the onset of diabetic complications (1). Nowadays, recent research has underlined the role of physical activity in the modulation of the immune and inflammatory response. Physical activity leads to a reduction in immunoglobulin secretion and modifies the balance between Th1/Th2 lymphocytes in favor of Th2 cells that secrete interleukin-10 (IL-10) compensating the inflammatory status caused by the disease (6). Altogether, the beneficial potential of physical activity in the control of type 1 diabetes seems to go beyond the mimetic effect of injected insulin, considering immunomodulation and anti-inflammation as new aspects to study.

Nevertheless, an intense area of research concerns the type, intensity and frequency of physical activity that each type 1 diabetic patient should perform in order to potentiate all the above-mentioned benefits. The majority of the studies support the idea that aerobic exercise in combination with resistance routines contributes to optimal reduction of glycosylated hemoglobin and improved glycemic control (7,8). In this sense, it is recommended to exercise 150 min/week in five sessions, at an intensity of 40-85% VO_2max or 55-90% maximal cardiac frequency. The protocol in each session includes 5-10 minutes of warm-up at the beginning, followed by the activity itself and 5-10 minutes of stretching at the end (9). Recently, high intensity interval training has been shown to exert similar benefits because it carries out a similar energetic expenditure than endurance exercises but in a shorter period of time (10).

However, a common limitation in the majority of the published studies regarding physical activity and diabetes management is the low number of participants (7,8). The result of such a limitation is that there is no clear consensus as to the recommended types of activities or sports for type 1 diabetic patients. Recently, the performance of sports practice in extreme environmental conditions has risen in popularity. Therefore, the objective of this study is to analyze the metabolic and inflammatory changes that a type 1 diabetic patient suffered after completing two extreme challenges. These include the exposure to a high altitude during an alpine expedition to the Himalaya and the performance of the physical probes that astronauts undergo for their specific preparation to go to outer space, such as acceleration, piloting and microgravity tests.

CASE REPORT

A 48-year-old male (165 cm height and 69 kg weight) participated in the study and gave his informed written consent. The intervention was approved by the Ethics Committee of Miguel Hernandez University (Elche, Spain) and met the legal requirements stated in the Declaration of Helsinki for research on human beings. Ten years before the intervention, the subject was a professional alpinist sponsored by different pharmaceutical companies being the first type 1 diabetic person that performed the circuit of the seven summits and reaching both poles (www.josufeijoo.com). During this period, the subject was very often exposed to extreme environmental conditions of temperature, partial oxygen pressure and physical and psychological stress. He prepared the different expeditions performing mainly aerobic activities consisting in long distance races and cycling. He declared that during mountain expeditions he did not follow a highly specific dietetic plan due to the difficulty to carry certain foods during ascensions.

Due to his abilities to perform tasks in extreme environments, he was recruited to participate in a program in the Yuri Gagarin Cosmonaut Training Center (Russia) to develop and investigate in new devices for telemedicine, particularly those with utilities in space missions. Thanks to this new project, he was the first type 1 diabetic astronaut in history. From this moment, diet and training routines were under supervision.

During training days, he performed a session of road cycling in the morning (1.5 h) and weight lifting (60-70% of the maximal weight lifted in only one repetition) in the afternoon (1 h). One day a week, he performed a surf training session in the beach (2 h) followed by a core training session (45 min) in the afternoon. The training protocol changed in certain weeks to avoid monotony, including long distance running (2 h), mountain cycling (2 h) or hiking (4 h) in the morning, followed by core training (45 min) in the evening. One day a week was for resting. His diet during training days consisted in 2,400-2,600 kcal, rich in carbohydrates (60-65%), 25-30% lipids and 10% proteins. The exercise was performed when glycaemia reached 180-200 mg/dl in order to avoid hypoglycemia episodes during exercise performance. Daily glycaemia was controlled by a long-acting insulin injection early in the morning and the injection of 3-4 units of immediate-acting insulin before exercise, according to the level of glycaemia. During the resting days, a 1,700 kcal diet was taken, consisting in 55% carbohydrates, 30% lipids and 15% proteins. Diet consumption was distributed in five daily intakes with two intakes after the two training sessions.

The objective of the intervention consisted in comparing the circulating metabolic and inflammatory parameters after a 22-day mountain expedition trek to the Everest camp base (5,364 m) and after different probes (6xg acceleration, microgravity and piloting) performed at the Yuri Gagarin Cosmonaut Training Center (Russia) the same year. Before both missions, a constant treadmill test was performed, consisting in 45 min running at 8-10 km/h. Glycaemia was monitored six times during the test at the beginning, three minutes, 13 minutes, 24 minutes, 36 minutes and at the end. Towards the end of the test, the speed slowed down to 4.8 km/h (passing from running to walking), allowing a correct manipulation of the subject for finger puncture during one minute, approximately. Initial glycaemia was 180 mg/dl at the beginning and descended gradually to 141 mg/dl at the end of the test. Cardiac frequency oscillated between 170-200 beats/min and the VO$_2$max was 48.7 ml/kg/min, considered to be optimal regarding the age and pathophysiological characteristics of the subject. Altogether, he was considered to be in the 90th percentile according to the criteria of the American College of Sport Medicine. During both challenges, the subject tried to maintain a stable glycaemia by eating certain supplements in specific moments in combination with insulin injections. The reported glycaemia during the alpine expedition oscillated between 110-140 mg/dl. Using a similar strategy during the different tests in the Cosmonaut Training Center, glycaemia oscillated between 122-145 mg/dl. No episodes of hypoglycemia were reported during both activities. In addition, the subject was conscious during the 45 minutes of the acceleration and piloting tests.

A total of three blood extractions were performed in fasting conditions. One extraction was performed the morning after a training day in order to monitor regular circulating parameters during the training period. The second extraction was performed after landing from the mountain expedition (seven days after reaching the base camp of the Everest). The third extraction was performed seven days after finishing the probes in the Cosmonaut Training Center. It is important to mention that we could not make the extraction just after finishing the extreme activities and for this reason several parameters presented a partial recovery that has to be taken into account during the interpretation of the results.

Regarding circulating cellular parameters (Table I), they all were in the healthy range. Only an increase in hematocrit was observed after the mountain expedition, coinciding with an increase in erythrocyte number. This could be due to the hypoxia undergone by the subject during the exposure to altitude as we have previously observed in healthy individuals (11). Regarding leucocytes, an increase in the number of neutrophils was observed only after the mountain expedition, coinciding with increased platelet number. This increase was not noticed after the probes in the Cosmonaut Training Center. Our interpretation is that the mountain expedition could be experienced as a stress situation by the subject that is better controlled during the probes in the Cosmonaut Training Center.

Regarding circulating biochemical parameters (Table II), glycaemia increased after the mountain expedition, coinciding with an increase in glycosylated hemoglobin. A higher glycaemia was observed after the probes in the Cosmonaut Training Center but was not accompanied by an increase in glycosylated hemoglobin. Therefore, this change was interpreted as a punctual anomaly during the moment of extraction. Regarding the lipid profile, the subject presents high levels of total cholesterol and triglycerides after both activities. Since the levels of HDL and LDL were in the healthy ranges, these results were interpreted as a consequence of the diet during the return trip and after completing the objectives. In addition, GPT and GGT increased slightly after the mountain expedition. CK was elevated as well, indicating a certain level of muscle damage, but this occurs very often in people making intense physical activity. Finally, plasmatic protein carbonyls were elevated after the mountain expedition due to the increased oxidative stress that involves the exposure to extreme altitude, as observed previously (11). The remaining circulating parameters were considered to be in the healthy range.

Regarding the cytokines (Table III), pro-inflammatory cytokines (IL-1β, IL-12p70, IFN-γ and TNF-α) were elevated during the training period, with the exception of IL-17a. A similar effect was observed in a previous report, in diabetic participants when exercising compared to type 1 diabetic sedentary volunteers (12). However, in the same study, the anti-inflammatory cytokines were elevated, most likely compensating the effect of the pro-inflammatory cytokines, while sedentary type 1 diabetic subjects presented lower levels of the anti-inflammatory cytokines IL-10, IL-13 and IL-22 (12). The diabetic astronaut presented a very similar pattern with high increases of IL-10, IL-13 and IL-22 after finishing both extreme activities, suggesting an optimal adaptation to the stress.

DISCUSSION

The subject studied in the present case declared often decompensations in glycaemia and in glycosylated hemoglobin in the period he was a professional alpinist. The entry in the Yuri Gagarin Cosmonaut Training Center program and the optimization of diet and training allowed to a better adaptation to extreme activities despite the disease. This is reflected by a correct control of glycaemia during the activities and the subsequent increase in circulating anti-inflammatory cytokines when both challenges were finished (Table III). Since blood extractions were not performed immediately after the execution of both activities, it was not possible to determine exactly the inflammatory status immediately after each challenge. We hypothesize a likely increase of pro-inflammatory cytokines, as observed during the training period. It must be mentioned that the subject generally performs physical activity in a hyperglycemic state and this stress could be activating pro-inflammatory cytokines. However, this stress is quickly compensated by the activation of an anti-inflammatory response, to which diet and training routine should contribute. In any case, this is a question that needs further investigation. In conclusion, extreme activities could be performed by type 1 diabetic subjects, but under a strict control of diet and training in order to favor an anti-inflammatory response. Nevertheless, this is a case report, and data interpretation must be made with extreme caution.

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Table I. Cellular circulating parameters determined in a regular training day (training), after the mountain expedition (post-mountain) and after the probes in the Cosmonaut Training Center (post-probes)

Parameters (units)	*Training*	*Post-mountain*	*Post-probes*
Erythrocytes ($x10^6/mm^3$)	5.3	5.6	5.2
Hemoglobin (g/dl)	16.2	16	15.5
Hematocrit (%)	47.2	49.4	45.3
MCV (fl)	89	88.5	87
MCH (pg)	30.5	28.6	29.8
MCHC (g/dl)	34.2	32.4	34.2
RDW (%)	12.4	13.7	14.2
Leucocytes ($x10^3/mm^3$)	5.4	7	5.7
Neutrophils ($x10^3/mm^3$)	3.1	4.4	3.0
Lymphocytes ($x10^3/mm^3$)	1.6	1.8	2.1
Monocytes ($x10^3/mm^3$)	0.5	0.6	0.3
Eosinophils ($x10^3/mm^3$)	0.1	0.2	0.2
Basophils ($x10^3/mm^3$)	0.1	0.1	0.1
Platelets ($x10^3/mm^3$)	278	359	262
MPV(fl)	8.4	9.2	9.2

MCH: mean corpuscular hemoglobin; MCHC: mean corpuscular hemoglobin concentration; MCV: mean corpuscular volume; MPV: mean platelet volume; RDW: red blood cell distribution width.

Table II. Biochemical circulating parameters determined in a regular training day (training), after the mountain expedition (post-mountain) and after the probes in the Cosmonaut Training Center (post-probes)

Parameters (units)	*Training*	*Post-mountain*	*Post-probes*
Glucose (mg/dl)	94	98	109
HbA1c (%)	8.7	9.1	8.5
Cholesterol (mg/dl)	195	211	230
HDL cholesterol (mg/dl)	86	70	79
LDL cholesterol (mg/dl)	95	100	94
Triglycerides (mg/dl)	71	209	283
Uric acid (mg/dl)	3.2	3.8	4.1
Creatinine (mg/dl)	0.83	0.73	0.73
Urea (mg/dl)	30	26	33
GOT/AST (U/l)	35	30	30
GPT/ALT (U/l)	29	45	37
GGT (U/l)	41	45	37
Alkaline phosphatase (U/l)	89	105	90
CK (U/l)	283	240	222
Iron (µg/dl)	68	64	71
Ferritin (ng/dl)	66	63	23
Na^+ (mmol/l)	146	145	138
K^+ (mmol/l)	4.8	5.3	4.2
Myoglobin (µg/l)	30.2	26.0	31.2
Lactate (mg/dl)	12	15	15
Protein carbonyls (µmols/l)	65,27	87.49	57.46

CK: creatine kinase; GGT: γ-glutamyl transpeptidase; GOT/AST: glutamate-oxaloacetate transaminase/aspartate transaminase; GPT/ALT: glutamate-piruvate transaminase/alanine aminotransferase; HbA1c: glycosylated hemoglobin.

Table III. Circulating cytokines determined in a regular training day (training), after the mountain expedition (post-mountain) and after the probes in the Cosmonaut Training Center (post-probes)

Cytokines (ng/ml)	*Training*	*Post-mountain*	*Post-probes*
IL-1β	13.23	3.71	3.71
IL-9	nd	nd	nd
IL-12p70	0.86	0.39	0.11
IL-17a	0.34	0.49	0.40
IFN-γ	5.12	3.55	2.07
TNF-α	7.95	5.84	5.07
IL-2	22.33	12.52	10.09
IL-4	9.77	8.76	8.98
IL-5	0.10	0.20	0.33
IL-10	nd	0.19	0.87
IL-13	10.01	9.42	10.00
IL-22	120.16	269.06	277.43

IFN: interferon; IL: interleukin; nd: non detected; TNF: tumor necrosis factor.