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Active Subjects With Autoimmune Type 1 Diabetes Have Better Metabolic Profiles Than Sedentary Controls

M. Adamo,*† R. Codella,*† F. Casiraghi,† A. Ferrulli,† C. Macrì,† E. Bazzigaluppi,§ I. Terruzzi,¶ L. Inverardi,‡ C. Ricordi,‡ and L. Luzi*†

*Department of Biomedical Sciences for Health, Università degli Studi di Milano, Milan, Italy
†Metabolism Research Center, IRCCS Policlinico San Donato, San Donato Milanese, Italy
‡Diabetes Research Institute, University of Miami Miller School of Medicine, Miami, FL, USA
§Laboraf-Diagnostic Research, San Raffaele Scientific Institute, Milan, Italy
¶Division of Metabolic and Cardiovascular Science, Metabolism, Nutrigenomics and Cellular Differentiation Unit, San Raffaele Scientific Institute, Milan, Italy

Previous studies in humans with type 1 diabetes mellitus (T1D) and in nonobese diabetic mice have investigated the beneficial immunomodulatory potential of aerobic physical activity. Performing high volume of aerobic exercise may favorably regulate autoimmunity in diabetes. We tested whether increased physical activity is a self-sufficient positive factor in T1D subjects. During a 3-month observational period, active (six males; 40.5±6.1 years; BMI: 24.5±2.1) and sedentary (four males, three females; 35.9±8.9 years; BMI: 25.7±3.8) T1D individuals on insulin pump therapy were studied for metabolic, inflammatory, and autoimmune parameters. At baseline and at the end of a 3-month period, glycosylated hemoglobin (HbA1c), autoantibodies (anti-GAD, anti-ZnT8, anti-IA2, and ICA) and proinflammatory cytokines (IL-6 and TNF-α) were evaluated. During the third month of the period, physically active T1D patients showed a significant reduction in the average glucose levels (–9%, $p=0.025$, by CGM) compared to the first month values, and even their hyperglycemic episodes (>180 mg/dl) diminished significantly (–24.2%, $p=0.032$ vs. first month). Moreover, active T1D subjects exhibited an improved body composition with respect to sedentary controls. No significant changes were detected as to the autoimmune and inflammatory profiles. This study confirms the beneficial role of physical exercise associated with insulin pump therapy in order to improve metabolic control in individuals with T1D. These preliminary positive observations need to be challenged in a prolonged interventional follow-up.

Key words: Physical activity; Type 1 diabetes (T1D); Continuous glucose monitoring (CGM); Insulin pump therapy

INTRODUCTION

Type 1 diabetes mellitus (T1D) is a disease characterized by an immune-mediated process that contributes to the depletion of insulin-secreting β-cells. The resulting insulin deficiency causes chronic hyperglycemia, leading to typical T1D long-term complications. Prevention of these complications is a primary goal in managing T1D. In fact, the evolution of the disease can positively change if, since its beginning, glycosylated hemoglobin is maintained at a level equal or lower than 7.0%[1]. At the diagnosis, most patients may have between 10% and 50% of normal pancreatic islet mass. Progressive destruction of β-cells accompanies the onset of the typical symptoms of T1D in genetically susceptible subjects: polydipsia, polyuria, and weight loss, even with increased appetite[2]. Following the initiation of insulin therapy, T1D patients may develop a phase called "honeymoon," during which residual β-cells transiently regain functionality[3], and patients need lower doses of insulin because of the relatively improved endogenous insulin secretion. Increasing insulin requirements are then needed to regulate blood glucose. Prevention of further β-cell destruction, through the modulation of autoantibody levels, is a pivotal clinical target in order to improve metabolic control and to lower hypoglycemic episodes and chronic complications[4]. In animal models of nonobese diabetic mice, the immunomodulatory therapy was able to slow or prevent the autoimmune process and the development of T1D[5]. Favorable results have also been shown in immunologic interventions on T1D patients using different immunosuppressive

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Address correspondence to Roberto Codella, Ph.D., Department of Biomedical Sciences for Health, Università degli Studi di Milano, Via F.lli Cervi 93, 20090 Segrate (MI), Italy. Tel: +39-02-503-30300; E-mail: roberto.codella@unimi.it

agents[6]. Physical activity, able to face oxidative stress and inflammation, has long been acknowledged as a cornerstone in the treatment of type 2 diabetes mellitus because of its insulin-sensitizer effects. On the other hand, before the discovery of insulin, T1D patients were limited in their ability to exercise because of the known risks of ketosis, dehydration, and management of multiple factors to maintain normoglycemia. After insulin therapy was introduced, a greater awareness was achieved as to the potential hypoglycemic events occurring postexercise. Recent studies discuss the health benefits of exercise in T1D patients[7,8]. However, improvements in insulin sensitivity can still lead to exercise-induced hypoglycemia. In order to reduce this risk, patients may lower their dose of short-acting insulin before exercise and eat carbohydrates before and during exercise[9]. Recent observations show that physically active T1D subjects, on a balanced caloric diet, have a better metabolic control with a residual endocrine pancreatic mass[10]. In a retrospective analysis of a T1D population, a subset of patients performing higher aerobic activity showed a reduced title of anti-glutamic acid decarboxylase (GAD) and anti-islet antigen 2 (IA2) compared to sedentary T1D patients[7]. These findings induced us to hypothesize that aerobic physical activity may positively regulate autoimmunity in diabetes, possibly by extending the honeymoon phase, while reducing daily insulin requirements and preventing diabetes-related complications. We tested this hypothesis in non-obese diabetic mice in a longitudinal study, confirming the immunomodulatory potential of aerobic physical activity[11]. This 3-month observational study focuses on the effects of different levels of physical activity on metabolic, inflammatory, and autoimmune parameters in T1D patients on insulin pump therapy.

MATERIALS AND METHODS

Study Design and Participants

Participants were recruited among T1D patients at the endocrinology outpatient clinic of Policlinico San Donato. Inclusion criteria were T1D, glycosylated hemoglobin <8%, and absence of comorbidities. Recruited subjects filled in the Physical Activity Readiness Questionnaire (PAR-Q)[12] and provided written informed consent prior to enrollment into this 3-month observational study. On the basis of the Baecke's exercise activity questionnaire[13], they were divided into two groups: sedentary (SED) and physically active (ACT) subjects, as shown in the flow diagram (Fig. 1). Thirteen T1D patients were enrolled out of the 20 participants initially screened, 7 sedentary (4 males, 3 females; 35.9±8.9 years; BMI: 25.7±3.8) and 6 physically active (6 males; 40.5±6.1 years; BMI: 24.5±2.1). They were all trained on how to use an insulin pump and continuous glucose monitoring (CGM). The study was approved by the clinical research ethical committee of Policlinico San Donato in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines.

Physicians were allowed to change antidiabetic medication regimens during the study, particularly to avoid hypoglycemic events. However, major regimen modifications were not necessary. A glucose level of ≤70 mg/dl was used to define hypoglycemia[14].

Analytical Procedures

Blood samples were drawn at baseline and after 3 months in order to acquire metabolic, autoimmune, and inflammatory profiles. Serum aliquots were stored at −80°C. All the samples were coded and rapidly transferred to the central laboratory of Policlinico San Donato, where the blood tests were performed.

Metabolic Parameters

The levels of plasma total cholesterol (TC), high-density lipoprotein-cholesterol (HDL-C), low-density lipoprotein-cholesterol (LDL-C), triglycerides (TG), blood glucose, C-peptide, glycosylated hemoglobin (HbA1c), and uric acid were determined.

Respiratory Indirect Calorimetry

After an overnight fast, the estimated resting energy expenditure (REE) was measured by indirect calorimetry (Quark RMR®; COSMED, Rome, Italy). The respiratory quotient (RQ) was calculated as the ratio between the volume of released CO_2 (VCO_2) and the volume of consumed O_2 (VO_2) derived from the oxidation of the substrates.

Body Composition

Body fat mass and fat-free mass were calculated on the basis of data obtained by Dual Energy X-ray Absorptiometry (Lunar DPX-L; Lunar Corp., Madison, WI, USA) using bioelectrical impedance analysis (BIA) at baseline and at the end of the 3-month study. The Tanita® BC-418 (Tanita Corp., Tokyo, Japan) measured body composition using a constant current at high frequency (50 kHz, 500 μA) supplied from the tips of the toes and the fingertips by means of eight electrodes. Voltage was measured on the calcaneus and the thenar eminence.

Autoimmunity and Inflammatory Parameters

The levels of the autoantibodies against zinc transporter 8 (anti-ZnT8), glutamic acid decarboxylase (anti-GAD), and tyrosine phosphatase-related islet antigen 2 (anti-IA2) were measured using the luminescent immunoprecipitation system (LIPS; Promega, Milan, Italy) as previously described[15]. Islet cell antibodies (ICA) were detected by indirect immunofluorescence in human pancreas. Interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α)

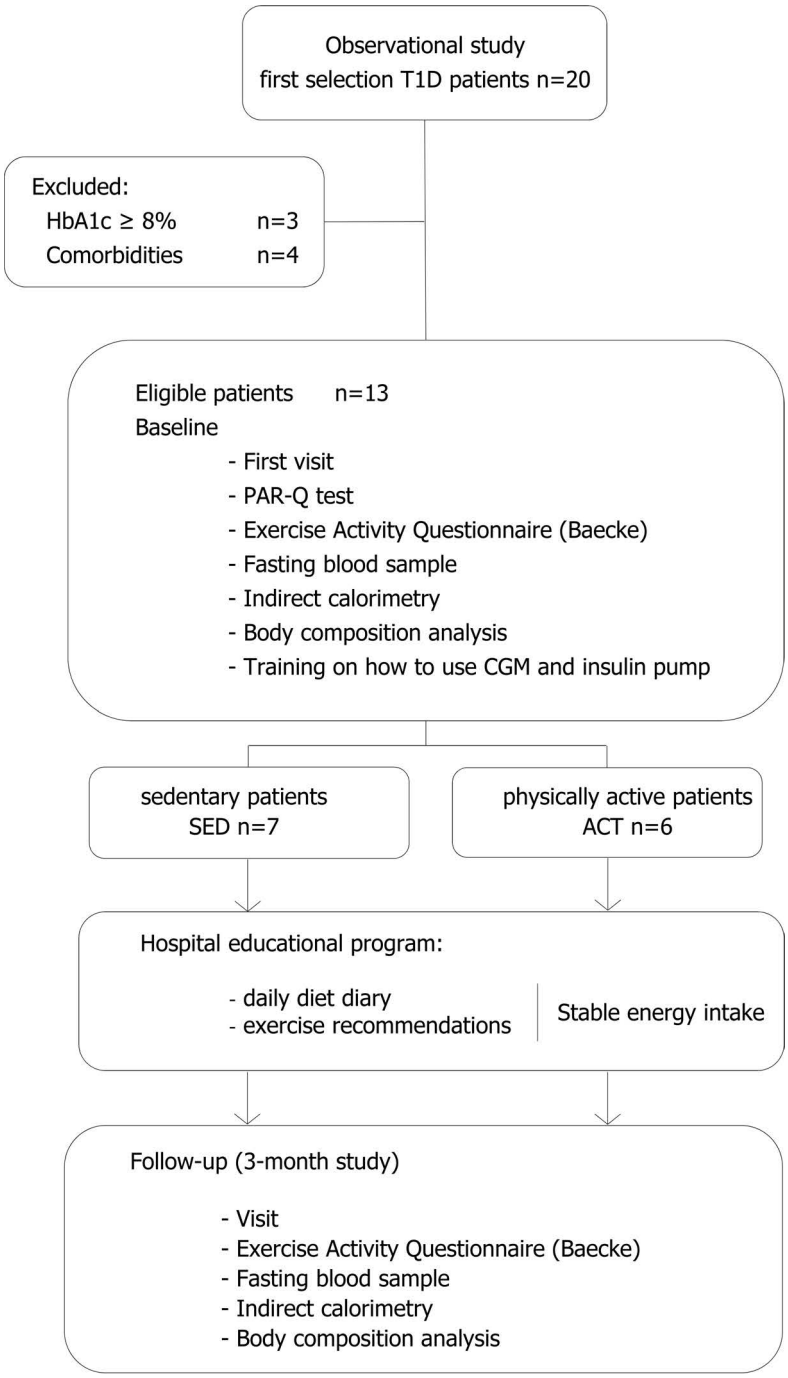

Figure 1. Flow diagram for study design and participants. Abbreviations: T1D, type 1 diabetes; HbA1c, glycosylated hemoglobin; PAR-Q, Physical Activity Readiness Questionnaire; CGM, continuous glucose monitoring; SED, sedentary group; ACT, physically active group.

were measured by enzyme-linked immunosorbent assay (ELISA; Affymetrix eBioscience, San Diego CA, USA).

Monitoring Devices

Participants, trained by a technician on the correct use of metabolic control devices, received an insulin pump (Animas Vibe®; Movi SpA, Milan, Italy) with infusion sets (Inset® II). They were also provided with a CGM device (Dexcom G4®; Movi SpA) with its weekly replaceable sensors. The insulin pump allows a very accurate administration of the insulin therapy, with a minimum infusion of 0.025 U/h in basal insulin regulation and a minimum increase of 0.5 U when infusing a bolus of insulin. The CGM consists of three parts: a small sensor placed on the

abdomen measures glucose levels up to 288 times/day, and a transmitter on top of the sensor wirelessly sends data (radiofrequency telemetry) directly to the monitor of the insulin pump, which is used as receiver. CGM provides interstitial fluid glucose levels using glucose oxidase-based electrochemical methods. Because of the lag time between blood and dermal interstitial glucose concentration, patients were asked to calibrate sensor glucose signals against corresponding blood glucose meter levels twice a day. Glucose levels measured by CGM were extrapolated by averaging readouts from the first and the third month of the study. The integrated system is equipped with acoustic alarms and a vibration mode; the device rings in case of hyperglycemia, hypoglycemia, and rapid increase or decrease of glucose levels. Insulin dosages and glucose levels were recorded by the device and uploaded by patients through weekly updates within an online program to let the physician monitor his patients.

Physical Activity Habits

Participants, either belonging to the SED or ACT group, were asked to maintain their physical activity levels—as assessed by Baecke's questionnaire[13]. However, staff supervision in the exercise physiology laboratory at the University of Milan was available to offer recommendations for safe and efficient exercise while ensuring stable energy intake throughout the entire 3-month study. For monitoring dietary intake, all participants filled in a daily diet diary.

Statistical Methods

Shapiro–Wilk statistical test was used to assess the distribution of variables. For normally distributed quantitative variables, Student's *t*-test was carried out. Mann–Whitney test was used to analyze non-Gaussian quantitative variables. Categorical variables were evaluated using Fisher's exact test. Data of each parameter, measured at baseline and after 3 months, were expressed as mean ± standard deviation (SD). Pearson's correlation test and linear regression analysis were also performed. For all tests, differences were considered statistically significant at $p \leq 0.05$. Analyses were carried out with the Statistical Package XLSTAT 2014, Excel 2010, and GraphPad Prism 7 (La Jolla, CA, USA).

RESULTS

Study Design and Participants

All T1D patients wore an insulin pump and a CGM sensor. Table 1 shows the study participants' characteristics and blood test changes after the 3-month observational period.

Metabolic Profiles

Daily glucose level fluctuations, observed in SED and ACT T1D patients, are shown in Figure 2A; ACT patients maintained a lower median glycemia throughout the 3-month period with respect to SED patients. During the third month, ACT T1D patients showed a significant reduction in the mean glucose levels measured by CGM (−9%, $p=0.025$) compared to the first month (Fig. 2B). Likewise, the frequency of detected glucose levels above 180 mg/dl significantly decreased in the ACT subjects after 3 months (−24.2%, $p=0.032$), while the frequency of detected glucose levels below 70 mg/dl increased compared to the first month (+34%, $p<0.01$). ACT patients self-administered a higher number of boli of insulin per day compared to SED controls (6.2±2.2 vs. 3.7±0.8 n boli/day, $p=0.056$). ACT maintained lower total insulin per day compared to SED patients either at baseline or at the end of the study (Table 1).

Respiratory Indirect Calorimetry

The indirect calorimetry proved a significant enhancement in the metabolism of SED patients compared to their baseline (REE: +7%, $p=0.04$).

Body Composition

The analysis of the body composition showed a significantly lower fat mass in the upper and lower limbs in ACT patients, compared to the SED patients (−50%, $p=0.045$) at the end of the 3-month time frame (Table 1). Glucose levels monitored by CGM and fat mass were correlated as outlined in Figure 3.

Physical Activity

After 3 months, the Exercise Activity Questionnaire[13] showed a significantly higher score in the Sport Index (+24%, $p<0.01$) and in the Physical Activity Index (+17.2%, $p<0.01$) among the SED patients compared to their baseline results.

Autoimmunity and Inflammatory Profiles

After 3 months of study, SED patients showed increased levels of IL-6 (+13.0%, $p=0.423$) and decreased levels of TNF-α (−15.3%, $p=0.625$) with respect to baseline, although not significantly. Among ACT patients, the concentrations of IL-6 and TNF-α were found stable throughout the study. The analysis of the autoantibodies showed a lower, although not significant, level of anti-GAD among ACT patients with respect to SED patients, both at baseline (−21.3%, $p=0.886$) and at the end of the 3-month study (−38.9%, $p=0.570$). No significant variations were shown, after 3 months of study, in the analysis of the other investigated autoantibodies (anti-ZnT8 and anti-IA2).

DISCUSSION

This study showed that being physically active is a per se factor improving glycemic control in T1D patients.

Table 1. Participants' Profiles and Changes

	SED ($n=7$)		ACT ($n=6$)	
	Baseline	3 Months	Baseline	3 Months
Age (Years)	35.9 ± 8.9		40.5 ± 6.1	
Men/Women	4/3		6/0	
Metabolic profile				
Fasting glycemia (mg/dl)	135 ± 45	119 ± 25	115 ± 23	125 ± 81
Glucose CGM (mg/dl)	159 ± 19	163 ± 28	149 ± 23	135 ± 14†
70–180 mg/dl	56.4% ± 18.2%	58.2% ± 14.2%	60.4% ± 8.4%	65.2% ± 6.8%
>180 mg/dl	37.0% ± 21.0%	35.4% ± 19.1%	31.4% ± 11.9%	23.8% ± 6.9%†
<70 mg/dl	6.6% ± 5.7%	6.4% ± 5.5%	8.2% ± 5.7%	11.0% ± 6.0%†
HbA1c (%)	6.8 ± 0.5	6.7 ± 0.4	6.5 ± 0.5	6.2 ± 0.4
(mmol/mol)	50.1 ± 6.1	50.0 ± 4.7	46.8 ± 5.4	44.7 ± 4.8
Insulin boli *n*/day	4.0 ± 2.6	3.7 ± 0.8	6.0 ± 2.9	6.2 ± 2.2
dose U/day	43.8 ± 24.4	54.4 ± 20.2	35.4 ± 8.8	38.6 ± 2.1
%basal	46% ± 12.3%	50.8% ± 12.8%	42.4% ± 6.1%	46.4% ± 5.1%
%boli	54% ± 12.3%	49.3% ± 12.8%	57.6% ± 6.1%	53.6% ± 5.1%
C-peptide (ng/ml)	0.18 ± 0.26	0.14 ± 0.20	0.05 ± 0.08	0.02 ± 0.01
Total cholesterol (mg/dl)	182 ± 39	201 ± 40	186 ± 36	180 ± 20
HDL-cholesterol (mg/dl)	65 ± 10	66 ± 19	72 ± 28	73 ± 28
LDL-cholesterol (mg/dl)	109 ± 23	111 ± 30	109 ± 43	105 ± 40
Triglycerides (mg/dl)	114 ± 115	189 ± 286	60 ± 34	52 ± 15
Uric acid (mg/dl)	3.9 ± 0.6	3.8 ± 0.9	4.1 ± 0.8	4.1 ± 0.6
Autoimmunity and inflammatory profile				
Anti-ZnT8 (A.U.)	14.7 ± 37.6	14.8 ± 37.6	12.1 ± 19.8	16.6 ± 21.3
Anti-GAD (A.U.)	27.0 ± 38.2	35.1 ± 45.2	21.3 ± 39.0	21.4 ± 39.0
Anti-IA2 (A.U.)	7.9 ± 20.2	9.4 ± 24.1	18.7 ± 18.8	20.7 ± 18.4
ICA (negative %)	57%	71%	50%	50%
IL-6 (pg/ml)	2.0 ± 1.5	2.3 ± 1.2	1.8 ± 0.0	1.8 ± 0.0
TNF-α (pg/ml)	5.9 ± 3.9	5.0 ± 0.0	5.0 ± 0.0	5.1 ± 0.2
Body composition (BIA)				
Weight (kg)	78.0 ± 16.6	78.2 ± 16.8	79.7 ± 5.1	79.7 ± 5.4
BMI (kg/m^2)	25.7 ± 3.8	25.3 ± 3.5	24.5 ± 2.1	24.5 ± 1.9
Total fat mass (%)	24.0% ± 11.7%	23.2% ± 12.7%	13.9% ± 2.7%	13.9 ± 4.1%
Total fat mass (kg)	19.6 ± 11.8	19.0 ± 12.2	11.1 ± 2.4	11.1 ± 3.5
Fat free mass (kg)	58.5 ± 10.6	59.1 ± 12.2	68.4 ± 4.3	68.7 ± 5.0
Fat mass % (trunk)	23.4% ± 11.7%	22.4 ± 13.7%	15.6% ± 3.5%	15.8% ± 5.6%
Fat mass % (limbs)	24.8% ± 12.9%	24.5 ± 12.8%	12.%5 ± 2.6%*	12.2% ± 2.3%‡
Skeletal muscle mass (kg)	15.7 ± 2.9	16.5 ± 4.8	18.3 ± 1.2*	18.4 ± 1.3
Indirect calorimetry				
VO_2 (L/min)	0.220 ± 0.036	0.238 ± 0.055*	0.241 ± 0.009	0.235 ± 0.038
VCO_2 (L/min)	0.188 ± 0.032	0.201 ± 0.040*	0.204 ± 0.009	0.196 ± 0.025
RQ	0.85 ± 0.03	0.85 ± 0.07	0.85 ± 0.06	0.84 ± 0.04
REE (kcal/day)	1550 ± 255	1671 ± 373*	1690 ± 51	1643 ± 256
REE %	92% ± 9%	98% ± 12%*	95% ± 7%	92% ± 11%

Sedentary (SED) and physically active (ACT) T1D patients at baseline and after 3 months of study. Values are expressed as mean ± SD. Glucose levels measured by continuous glucose monitoring (CGM) are extrapolated by averaging readouts of the first and the third month of the study for "baseline" and "3 months," respectively. BIA, bioelectrical impedance analysis; BMI, body mass index; RQ, respiratory quotient; REE, resting energy expenditure; VCO_2, volume of released CO_2; VO_2, volume of consumed O_2.

*$p \leq 0.05$ versus SED baseline; †$p \leq 0.04$ versus ACT baseline; ‡$p \leq 0.05$ versus SED 3 months.

During an observational period of 3 months, ACT subjects' glycemic values were lower than SED controls as indicated by the CGM. In addition, glycosylated hemoglobin, the main measure of the glycemic control, tended to be better in the ACT group, at baseline and after 3 months, with respect to their SED counterparts. Low levels of HbA1c are associated with low requirements of exogenous insulin. It is ascertained that exercise increases

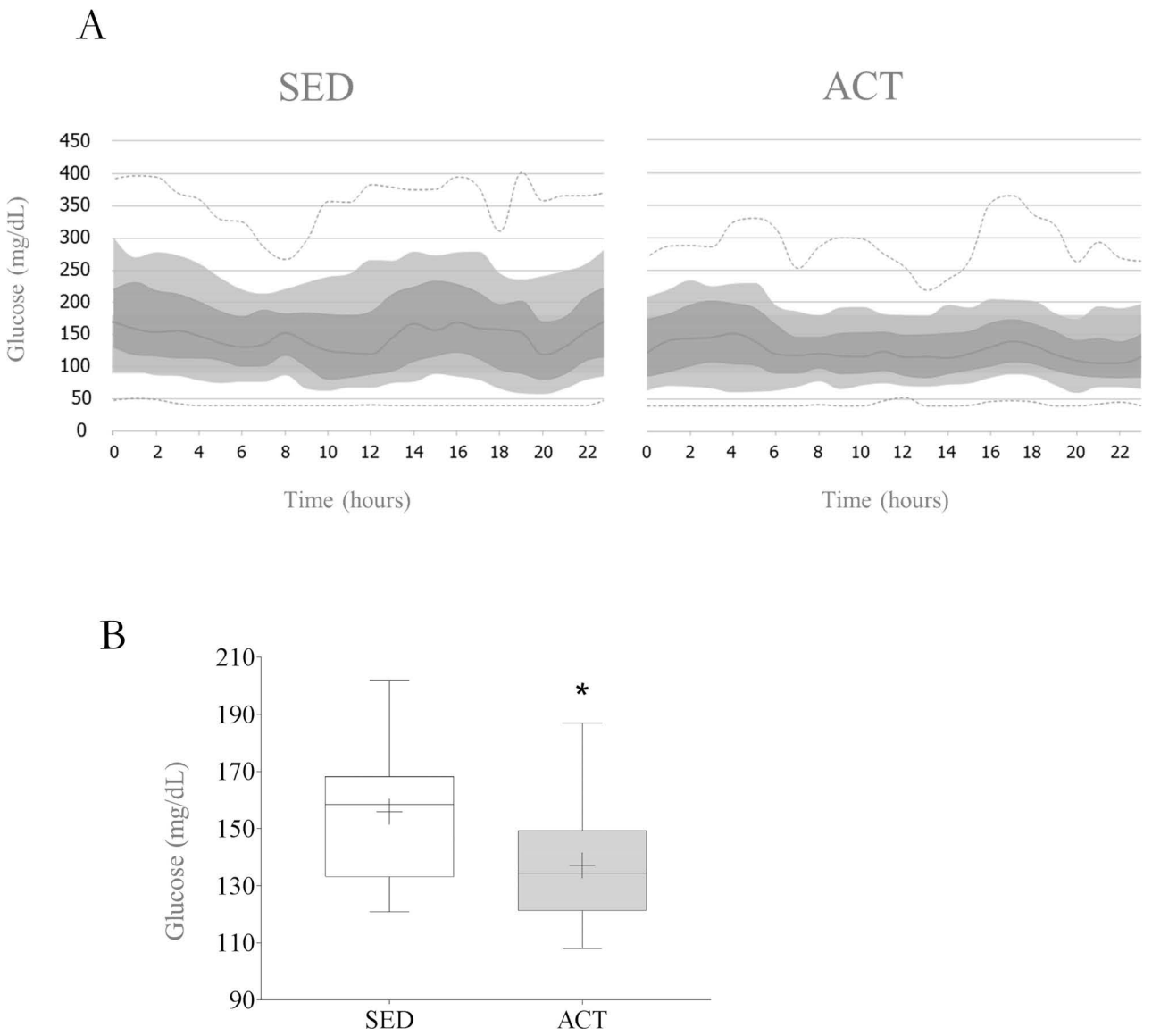

Figure 2. (A) Daily glucose fluctuations in sedentary (SED) and physically active (ACT) type 1 diabetes (T1D) patients throughout the 3-month study. The middle line indicates the median glucose levels measured by CGM. The dark gray area is bounded by the most common glucose measurements (25th to 75th percentile). The lighter gray area is enclosed between the least common values (10th to 90th percentile). The dotted line shows the lowest and highest glucose values. (B) Box-and-whisker plot comparing glucose levels measured by continuous glucose monitoring (CGM) in SED and in ACT T1D patients during the third month of the study. *ACT patients show a significantly lower mean (−9%, $p=0.025$) compared to the SED patients. The mean is identified by the "plus" sign. The horizontal line within the box indicates the median, the upper and lower limits of the boxes, the interquartile range, and the ends of the whiskers 1.5 times the interquartile range.

insulin sensitivity and improves β-cell efficiency and glucose utilization[16,17]. These physiological mechanisms have also been proven in T1D patients. These effects could be favored using an insulin pump[17] integrated with a CGM system. Introduced in the late 1970s, the insulin pump, also known as continuous subcutaneous insulin infusion (CSII), is still the gold standard of T1D therapy[18], as it is able to simulate the physiologic pancreatic secretion of insulin by delivering rapid-acting insulin analogs throughout the day. While multiple daily insulin injections (MDII) and CSII are both considered effective, the latter offers a greater flexibility, allowing a tighter and more accurate insulin administration even for small quantities[19]. In fact, management of T1D is essential to prevent complications and allow a quality of life similar to the nondiabetic population[20].

Moreover, in T1D, the insulin-producing β-cells face a destruction process in which T cells play a central role.

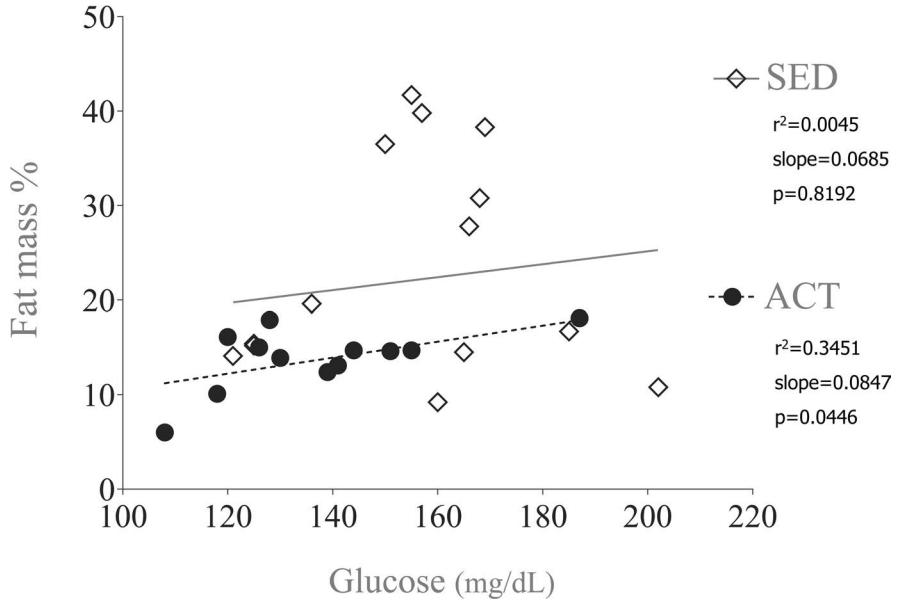

Figure 3. Linear correlation between glucose levels, measured by continuous glucose monitoring, and fat mass percentage in physically active patients (ACT; black circles) compared to sedentary controls (SED; blank diamonds).

In fact, T1D is characterized by an imbalance in the Th1/Th2 cytokine ratio. This imbalance may be skewed toward an excess of Th1 cytokines, whereas Th2 cytokines are deficient[21] (Fig. 4A).

We hereby focused on two particular exercise-modulated cytokines: IL-6 and TNF-α. It is now acknowledged that IL-6 is released by myocytes after exercise; IL-6 induces lipolysis and gene transcription in adipose tissue[22]. TNF-α, a proinflammatory cytokine released by adipocytes, is correlated with insulin resistance[23]. Muscle-derived IL-6, by inducing the production of IL-10, indirectly inhibits TNF-α[7]. Fischer observed elevations in IL-6 after intense exercise; this effect is considered a positive factor in modulating the immunological and metabolic responses to exercise[24]. IL-6 is therefore capable to modulate the beneficial exercise effects as it restores the Th1/Th2 equilibrium (Fig. 4B). Another study showed that the anti-inflammatory effect of exercise, mediated by the upregulation of Th2 cytokines, may lead to a protective response toward the autoimmune process directed to β-cells[25].

Among SED patients, a slight increase in IL-6 and a small decrease in TNF-α, even if not significant, may show a favorable tendency toward an anti-inflammatory pattern in our study. Inflammatory and autoimmunity profiles resulted beneficially modified in other previous studies[6,7], probably due to specific exercise intervention setting.

Modification of body composition is typically debated in type 2 diabetes as a main feature of several metabolic

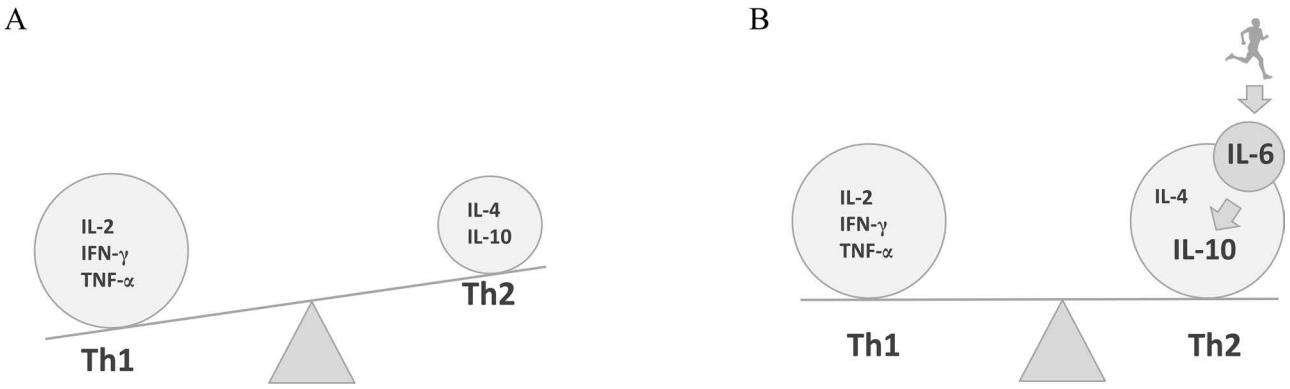

Figure 4. (A) Type 1 diabetes is an immune-mediated process characterized by an imbalance in the Th1/Th2 cytokine ratio. This balance is skewed toward an excess of Th1 cytokines (IL-2, IFN-γ, and TNF-α), whereas Th2 cytokines (IL-4 and IL-10) are deficient. (B) Muscle-derived IL-6 induces the production of IL-10, which inhibits TNF-α, a proinflammatory cytokine. IL-6 is therefore capable to elicit the beneficial exercise effects as it restores the Th1/Th2 equilibrium.

disorders. Yet, T1D subjects often exhibit a mass remodeling detrimental to their metabolism[26]. In our study, a moderately linear correlation between glucose levels and fat mass was found in the ACT individuals, confirming the enhanced glucose disposal exerted by the augmented muscle mass. In the European Prospective Investigation into Cancer and Nutrition Study (EPIC)[27], the greatest reductions in mortality risk were observed between the two lowest activity groups. This suggested that efforts to encourage even small increases in activity levels of sedentary individuals may be beneficial to public health. Thus, behavioral strategies favoring an increase in physical activity, as well as a reduction in sedentary time, may be successful also for T1D patients. As expected, ACT subjects exhibited better lipid profiles than those in the sedentary condition. However, the difference was nonsignificant. Lipid metabolism is another key point when discussing exercise-related fuel metabolism in T1D individuals; the relevant literature, in fact, is still controversial[28]. Supraphysiological insulin levels may impair hepatic glucose output and limit the physiological shift from glucose to fatty acid oxidation during exercise. Even though fatty acid oxidation was not measured in this study, lipid metabolism seemed not to be impaired in ACT people compared to SED, especially considering their TG levels.

The loss of insulin secretion regulation and the consequent need of exogenous insulin predispose to an increased risk of exercise-associated glucose fluctuations in individuals with T1D. This study magnified the risk of hypoglycemic events even under the strict control of CSII plus CGM. This risk, in fact, cannot be utterly abolished. Nonetheless, pump therapy represents one of the most cost-effective approaches in different populations with T1D[29]. Hypoglycemia is a relevant barrier for being physically active in T1D individuals; exercise professionals should promote not only greater awareness of hypoglycemic/hyperglycemic events during exercise but also the potential side effects of suboptimal glucose control. Few studies have explored diversified strategies to prevent hypoglycemia in exercising T1D people. Some exercise studies on T1D subjects consider carbohydrate supplement[30], reduction of preprandial insulin doses[31], and adjustment of basal insulin infusion in pump therapy[32]. Other studies suggest to perform intermittent, very brief (about 10 s) maximal intensity sprints either at the beginning[33] or at the end[34] of a moderate intensity exercise session: the hypoglycemia would be attenuated by a transient reduction of glucose disposal[35]. Another strategy would consist in performing resistance exercise prior to aerobic physical activity[36]. On the contrary, hyperglycemic episodes may occur following strenuous exercise; in this case, a small bolus of a short-acting insulin analog is suggested, or, for insulin pump users, basal insulin infusion may be temporarily increased to restore euglycemic levels[34]. At the end of this 3-month observational period, hyperglycemic events significantly diminished with respect to baseline in the ACT group, despite a putative stress due to exercise; this could be interpreted as another cue of a well-controlled monitoring system. Besides, ACT patients, compared to SED ones, seemed to have a more responsible behavior in the monitoring of glucose levels, as witnessed by a favorable ratio between boli and doses of infused insulin.

At the hospital outpatient clinic and in the exercise physiology laboratory, counseling sessions were successfully offered to both groups in the management of the disease. Therefore, an educational program addressed to T1D patients focused on insulin injection monitoring, diet and exercise are strongly recommended. As suggested by our indications, especially SED patients may benefit from an augmented level of exercise habits by following the exercise staff recommendations.

The main limitation of this study is the small sample size. An interventional study would have possibly allowed to detect significant differences between groups in some features (HbA1c, insulin doses, and lipid profiles). However, we think that this snapshot is still informative within the T1D scenario. Likely, our findings, even if limited, can be attributed to the different physical activity levels. Greater changes rather than tendencies might be gathered with a controlled exercise trial. As such, these observations may be meant as primary predictors of the exercise-induced metabolic improvements in T1D subjects. Future studies should address whether exercise training may impact also on autoimmunity beyond inflammatory pattern in individuals affected by T1D or pre-T1D.

CONCLUSIONS

This study highlights that exercise is an independent factor for better metabolic profiles in T1D individuals on insulin pump therapy. Integrated monitoring systems (CSII plus CGM) along with an educational-based approach are efficient in gaining the beneficial effects of exercise in the management of T1D. Further interventional studies are advocated for investigating a positive exercise-induced immunomodulation.

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