research letter

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Exercise training improves physical fitness and vascular function in children with type 1 diabetes

Children with type 1 diabetes mellitus (DM1) show endothelial dysfunction and mild artery wall thickening compared to their age-matched healthy peers. In this study, we examined the effect of 18-week exercise training on physical fitness and vascular function and structure in children with DM1. We examined physical fitness, brachial artery endothelial function [flow-mediated dilation (FMD)], common carotid artery diameter, wall thickness and wall-to-lumen ratio before and after 18-week exercise training in children with DM1 ($n = 7$). Physical fitness, measured as maximal oxygen consumption, improved after training ($p = 0.039$). Brachial artery FMD improved from 7.5 ± 4.2 to 12.4 ± 5.2 ($p = 0.038$). Carotid artery diameter, wall thickness and wall-to-lumen ratio did not change significantly ($p = 0.26$, 0.53 and 0.27, respectively). We showed that exercise training in children with DM1 effectively reverses endothelial dysfunction and improves physical fitness. These data emphasize the important role for physical activity in the management of DM1.
Keywords: cardiovascular disease, cardiovascular risk, exercise, diabetes complications, diabetes mellitus type 1, flow-mediated dilatation

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RESEARCH LETTER

Introduction

Atherosclerosis starts early in life and is accelerated in patients with type 1 diabetes mellitus (DM1) [1]. These vascular changes contribute to an early development of cardiovascular diseases. Endothelial dysfunction is considered as an integral manifestation of vascular disease which precedes atherosclerosis and predicts cardiovascular events [2]. Already at a young age, children with DM1 show an impaired endothelial function [3,4]. Also, structural changes are reported in children with DM1, such as an increase in carotid artery wall thickness [3], which is regarded as an early sign of atherosclerosis and is strongly related to the occurrence of future cardiovascular events [5].

Exercise training reduces primary and secondary cardiovascular events [6], which is, at least partly, mediated through the direct effects on vascular function and structure [6]. Exercise training in adults with DM1 improves endothelial function [7]. Although a recent cross-sectional study suggested a strong link between physical activity level and vascular function in children with DM1 [8], no previous study directly examined the impact of exercise training on the vasculature in children with DM1. Therefore, we examined the effect of 18-week exercise training on vascular function and structure in children with DM1. We expect that exercise training improves endothelial function and decreases wall thickness in children with DM1.

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Methods

Subjects

We included nine DM1 children (10.9 ± 1.5 years, 4 boys : 5 girls) in our study, who had a mean duration of DM1 of 2.7 $\pm$ 3.1 years and glycated haemoglobin (HBA1c) levels of 63 $\pm$ 12 mmol/mol. All children were aged between 8 and 12 years. Children with DM1 were recruited from the Children Diabetes Centre Nijmegen, the Netherlands, and were diagnosed with DM1. We excluded children with DM2, cardiovascular pathology, mental retardation and contra-indications for physical exercise. The study was approved by the Ethics Committee of the Radboud University Nijmegen Medical Centre, adhered to the Declaration of Helsinki and all subjects gave prior written consent.

Experimental Design

Before and after the 18-week intervention, subjects reported on two different occasions to our laboratory. First, body characteristics (height, weight and waist circumference) were measured, followed by a maximal running test. On the second day, vascular measurements (brachial artery endothelial function and carotid artery wall thickness) were performed in all children after a 3-h fast and 24-h abstinence from exercise, caffeine and vitamin C.

Experimental Procedures

Body Characteristics. We examined weight (SECA-7701321004 weighing scale), height (SECA D.B.G.M. stadiometer) and waist circumference. All measurements were performed twice (with using the mean value) and performed by a single, experienced researcher.

Physical Fitness. Physical fitness was calculated as the peak oxygen uptake ($VO_{2\,max}$) during a maximal, exhaustive running test using the Bruce-protocol. Spiro-ergometric equipment (Quark CPET, Cosmed, Italy) was used to continuously measure oxygen uptake. A chest band continuously recorded heart rate. A 3-lead electrocardiogram was used to observe heart rhythm during the test.

Brachial Artery Endothelial Function. Patients rested supine in a temperature-controlled room (22 ± 0.5 °C). A cuff was positioned distal to the olecranon process. A 10-MHz multifrequency linear array probe attached to a high-resolution ultrasound machine (T3000, Terason, Burlington, MA, USA) was used to image the brachial artery. A detailed description of the protocol is found elsewhere [9]. After a resting period of at least 20 min, baseline measurement of the brachial artery diameter and blood velocity was performed. This was followed by a 5-min inflation of the blood pressure cuff to >200 mmHg. Postdeflation recording of brachial artery diameter and velocity was performed for 3 min. Post-test analysis was performed using custom-designed edge-detection and wall-tracking software which is independent of investigator bias.

Carotid Artery Wall Thickness. Baseline wall thickness and diameter of the common carotid artery were measured using high-resolution ultrasound machine (T3000). The left common carotid artery was measured 2 cm proximal to the bulbus [5]. Ultrasound parameters were set to optimize longitudinal, B-mode images with a specific focus on the far-wall. Data were recorded in three different planes using a recording of at least 10 s. Post-test analysis was performed using custom-designed, semi-automated edge-detection and wall-tracking software which is independent of investigator bias.

Intervention

The intervention consisted of an 18 weeks exercise training program with predominantly running exercise at a frequency of two times a week. The first training of each week was guided by an athletic coach, whereas the second training was performed individually at home. Exercise involved lower limb exercise only. The guided exercise session involved 30 min of running exercise (intervals) and 30 min of group-based activities (such as ball games, short relay races, running techniques and stretching). The individual exercise session at home involved 30 min of interval running and a 10-min warm-up and cooling down (including stretching).

Statistics

Statistical analyses were performed using SPSS 17.0 (SPSS, Chicago, IL, USA) software. All data are reported as mean ± SD and statistical significance was assumed at $p < 0.05$. Paired *t*-tests were used to examine the effect of exercise training on our primary outcome parameters.

Results

Two children with DM1 did not finish the study and were not included in the analysis. Children showed increased height and weight, while no change in body mass index (BMI) and waist circumference was observed after exercise training (Table 1). Peak oxygen consumption improved significantly after training (Table 1). Maximal heart rate (HR) at peak oxygen consumption did not change after exercise training (Table 1).

Table 1. Subject characteristics, physical fitness and carotid artery characteristics of children with diabetes mellitus type 1 (DM1, n = 7), before (pre) and after (post) the 18-week intervention.

Variable	Pre	Post	p-value
Height (m)	1.48 ± 0.12	1.50 ± 0.12	0.002
Weight (kg)	37.6 ± 10.0	38.6 ± 10.4	0.199
BMI (kg/m^2)	17.0 ± 2.4	16.9 ± 2.3	0.769
Waist circmference (cm)	62.2 ± 6.2	61.4 ± 5.7	0.356
Time-to-exhaustion (s)	609 ± 104	655 ± 100	0.139
$VO_{2\,max}$ (mlO$_2$/kg/min)	44.0 ± 5.9	46.0 ± 5.1	0.039
Maximal heart rate (beats/min)	200 ± 9	198 ± 6	0.664
Carotid artery			
Diameter baseline (mm)	5.1 ± 0.4	5.3 ± 0.1	0.26
Wall thickness (mm)	0.44 ± 0.09	0.41 ± 0.09	0.53
Wall-to-lumen ratio	0.09 ± 0.02	0.08 ± 0.02	0.26

Data are presented as mean ± SD. p-values refer to a paired *t*-test to examine the effect of the 18-week intervention.

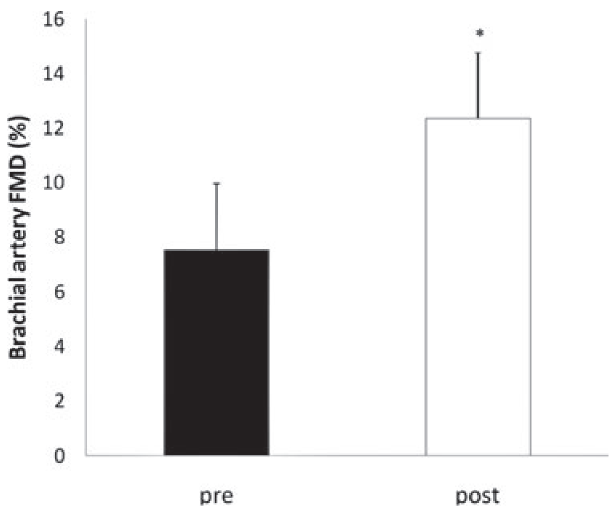

Figure 1. Brachial artery flow-mediated dilation (FMD, presented as the absolute change from baseline) in children with type 1 diabetes mellitus (n = 7) before (pre) and after (post) 18-week exercise training. Error bars represent standard error. *Significantly different from pretraining at <0.05.

Vascular Function

Brachial Artery Endothelial Function. A significant increase in FMD was observed after training (figure 1). Baseline diameter was not different before and after training (2.61 ± 0.55 and 2.64 ± 0.41 mm, respectively, p = 0.90).

Carotid Artery Wall Thickness. We found no effect of the intervention on common carotid artery diameter, wall thickness or the wall-to-lumen ratio (Table 1).

Discussion

The main finding of this study is that 18-week exercise training, including two exercise sessions per week, effectively improves physical fitness and endothelial function in children with DM1. Impaired endothelial function, which is present in children with DM1 already at a very young age [3,4], is regarded as an integrative part of the atherosclerotic process and is predictive for future cardiovascular events [2]. The improvement in brachial artery endothelial function after training in children with DM1 suggests that exercise training decreased the risk for future cardiovascular disease. These findings confirm a recent cross-sectional study that found a strong link between physical inactivity and endothelial dysfunction in DM1 [8]. Thus, a modest increase in physical activity level is sufficient to improve endothelial function in children with DM1, but also suggests a causal role for physical inactivity to induce endothelial dysfunction.

Increased conduit artery wall thickness is related to an increased cardiovascular risk [5]. However, exercise training did not alter carotid artery wall thickness. One possible explanation is that the duration of DM1 in our cohort was insufficient to develop wall thickening before training or that the duration of training was too short for structural wall remodelling. Although previous studies found carotid artery wall thickening in children with DM1, these studies examined older cohorts, with a longer duration of DM1 [3]. Indeed, a recent study found that endothelial dysfunction precedes the 6-year progression in wall thickness [10], which indicates that time is needed for carotid artery wall thickening to develop. In addition, 6-week exercise training in childhood obesity had no effect on carotid artery wall thickness, while continuing this type of training for 1 year significantly reduced wall thickness [11].

In summary, children with DM1 are placed at increased risk to develop cardiovascular complications later in life, with the development of cardiovascular abnormalities starting early in childhood. Our study indicates that exercise training can improve endothelial function in children with DM1, supporting a causal link between physical activity and endothelial (dys)function. Moreover, our finding indicates the importance of physical activity in the daily management of children with DM1 to prevent future cardiovascular morbidity and mortality. We recommend future studies to further examine the potential link between physical (in)activity and vascular (dys)function in children with DM1.

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Conflict of Interest

M. H. and M. N. designed this study. J. S., M. C., D. T. and K. N. conducted the experiments. J. S., D. T., M. H. and M. N. analysed this study. J. S., D. T., K. N., M. H. and M. N. wrote the manuscript. All the authors have no competing interests.

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