Introduction

Type 1 diabetes is a chronic metabolic disorder with absence or relative deficit of circulating insulin, which is associated with a chronic elevation of blood glucose and glycosylated end products and an increased cardiovascular risk [1,2]. Theoretically, treatment of type 1 diabetes requires a careful balance among caloric intake, physical activity and insulin replacement [3] to sustain normalization of blood glucose [4].

To improve health and reduce risk for chronic disease, the American College of Sports Medicine [5] published guidelines for healthy adults stating that 20-60 minutes of medium intensity of continuous or intermittent aerobic activity three to five times per week is needed for developing and maintaining cardiorespiratory fitness, body composition and muscular strength [6]. Strength training should be an integral part of the training program, and therefore new guidelines have been published by the ACSM suggesting that untrained people should train the entire body with 1-3 sets of 8-12 repetitions at intensity of 60-70% of one-repetition maximum (1RM) 2 to 3 days per week [5]. The US Department of Health and Human Services also has published physical activity guidelines for children and adolescents [7] which state that 60 minutes of moderate physical activity most days of the week is necessary for the prevention of weight gain, for weight loss, or for sustaining weight loss. Contradictory data have been reported regarding the benefits of supervised exercise training on metabolic control in children and children with type 1 diabetes.. Most studies examining the effects of exercise training on cardiovascular fitness and glycaemic control in children and adolescents with type 1 diabetes have used aerobic activity as intervention [4,8,9,10,11,12]. Campaign et al. [8] and Dahl-Jorgenson et al. [9] reported decreased levels of HbA1c after aerobic training 3 times resp. 2 times a week, for 12 weeks resp. 5 months, each session lasting 30 minutes resp. 60 minutes. Landt [et al.] [11] and Wallberg-Henriksson et al. [13] reported no changes in HbA1c after aerobic training 3 times a week, for 12 weeks, each session lasting 45 minutes, but found an increased insulin sensitivity after an euglycemic clamp. Laaksonen et al. [10], Rowland et al. [12] and Zinman et al. [4] reported no decrease in glycated haemoglobin levels or insulin dose after an endurance training program 3 times a week, for 12 to 16 weeks, each session lasting 30 to 60 minutes. Only 3 studies have investigated the effect of strength exercises or a combination of aerobic and strength training on metabolic fitness in type 1 diabetes patients [14]. Ramalho et al. [15] reported no beneficial effects on HbA1c after resistance training 3 times a week, for 12 weeks, each session lasting 45 minutes, but found a reduction in the daily insulin dose. Mosher et al. [16] showed beneficial effects on glycated haemoglobin in type 1 diabetes patients after both aerobic and resistance training, but Heyman et al. [17] observed no change in daily insulin requirement or HbA1c. In the first study participants exercised 3 times a week for 12 weeks each session lasting 45 minutes and in the second study they exercised twice a week for 6 months each session lasting 120 minutes.

Quality of life is strongly associated with glycaemic control [18]. Regarding the effect of exercise training on quality of life only one study has been performed. Wiesinger et al. [19] noted in patients with longstanding diabetes improved subscores of quality of life, mainly in social functioning and vitality, after endurance training twice a week for 4 months.

The unanswered question as to whether exercise should be encouraged in subjects with type 1 diabetes in order to achieve better glycaemic control is important with respect to reduced risk of diabetic complications. Therefore, the aim of this study was to evaluate the effect of 20 weeks of a combined aerobic and resistance training on glycaemic control, cardiovascular fitness and quality of life in adolescents with type 1 diabetes patients.

Materials and methods

<u>Study participants</u>

Adolescents (ranging from 10 to 18 years) with type 1 diabetes with a disease duration of at least one year, and with at least a pubertal development of Tanner stage M2 (breast development and first appearance of pubic hair) for girls and G2 (testicular volume of more than 3 ml) for boys and living no further than 15 km of the hospital were recruited for this study. From 140 adolescents with type 1 diabetes, registered at the Department of Pediatric Endocrinology and Diabetology of the University Hospital Ghent, 55 met all criteria stated above. From only 16 subjects, an informed consent, signed by adolescent and parents, was obtained (Fig. 1). These participants were equally assigned to intervention or no intervention by using random allocation with sealed envelopes.

<u>Intervention program</u>

The intervention group followed a 20 week training program containing aerobic and strength exercises. The children exercised twice a week during 70 minutes. The training was supervised by physiotherapists.

Each training session included a warming up (5 minutes), strength training of upper limbs (10 minutes), strength training of lower limbs (10 minutes), strength training of abdominal muscles (10 minutes), cycling (10 minutes), running (10 minutes), stepping (10 minutes) and cooling down (5 minutes).

The aerobic part of the training (cycling, running and stepping) involved individually prescribed exercise regimens starting at 60% of heart rate reserve calculated from peak heart rate (HR), which increased up to 70% after 6 weeks and to 75% after 12 weeks. The participants used stationary bicycles, treadmill and cross trainers.

Strength exercises were performed using stack weight and fitness equipment (biceps, triceps, leg press and adductor). Intensity of strength training was calculated from the 1 repetition maximum (1RM)-values. The starting level was 20RM, which increased up to 12RM. In the first 12 sessions, each session consisted of 2 sets of 15 repetitions at 20RM. In the next 12 sessions, 2 sets of 12 repetitions at 17RM were done. In the final 8 weeks, 3 sets of 10 repetitions at 12RM were done. Between two sets a resting period of 60 seconds was minded.

Concerning the abdominal muscles functional exercises were done. The children lay down on their back and performed 2 sets of 20 sit-ups. They have done the exercises with knees up, knees down to the right and knees down to the left.

The children in the control group participated in their daily normal activities, but did not participate in a supervised exercise program.

Measurements

The measurements of the examined variables were done by blinded assessors. They examined the participants without being aware of the programme followed by each individual.

Before and after the training program, children were tested for the following variables:

1 Body size and body composition

Height was measured to the nearest 0.1 cm using a stadiometer (Holtain Ltd., UK). Weight was measured to the nearest 0.1 kg on a digital balance scale (Seca, max. 200 kg, Germany) with the subject wearing lightweight clothing and no shoes. BMI was calculated from weight and height. Waist circumference was measured by a tape meter with a tension rod to assure accuracy at the level of the umbilicus. Body composition was assessed by bio-impedance (Bodystat 1500 MDD, Euromedix, Belgium). Patients were in supine position for at least 5 minutes. Surface electrodes were attached to the hand respective the foot. Fat mass (FM) and fat free mass (FFM) were calculated using the formula of Schaeffer et al. [20].

2. Serum analyses

Venous blood samples were collected in tubes containing EDTA for the HbA1c determination or sodium fluoride for the plasma glucose assay after a 12-hour overnight fast. Plasma glucose was measured via the glucose oxidase method using a Beckman Glucose Analyser. HbA1c results were determined with the ion-exchange high-performance liquid chromatography (HPLC) method using a Menarini HA-8140 analyzer.

Blood samples were taken before the onset of the 20 week training program and 48 hours after the last exercise session, the latter to prevent a carryover effect from the last exercise bout.

3 Physical fitness

3.1 Maximal cardiopulmonary exercise test

Peak oxygen uptake was assessed during graded exercise using a fully automated ergospirometry system (Oxycon Pro Jaeger) with integrated 12-lead ECG (Marquette) and cyclo-ergometer (Ergoline Ergoselect 100K) [17]. Subjects were encouraged to perform exercise testing to the self-determined limits of their functional capacities or until the physician stopped the test because of severe adverse events, such as increasing chest pain, dizziness, potentially life-threatening arrhythmias, clinically important ST-segment deviations, marked systolic hypotension, or hypertension. Patients cycled at a pace of 60 rpm. A 'ramp'protocol was used, starting at a workload of 0 Watt and increasing continuously with a ramp (in W/min) calculated by body weight divided by 4. After reaching peak exercise, patients recovered for 8 minutes while pedalling continuously at a very low frequency and a workload equivalent to the one used at 1 min of exercise. Twelve-lead ECG and heart rate were recorded continuously during the test, whereas blood pressure was recorded every 3 minutes during the exercise phase and every 2 minutes during the recovery phase with an integrated blood pressure monitor (SunTech Tango). Standard ventilatory and respiratory gas exchange parameters (VO2, VCO2, Ventilation) were obtained by dynamic breath-by-breath measurements in open system. PeakVO2 was expressed as the highest attained VO2 during the final 30 seconds of exercise, peakHR and peakWatt was taken at the moment of peakVO2 according to the American Thoracic Society (ATS) guidelines [21].

3.2 Six-minute walk test (6MWT)

All patients performed a standardized, self-paced 6MWT in a 20-meter long corridor. Instructions to patients were given according to accepted recommendations. They were asked to cover as much distance as possible within 6 minutes without running. Patients were allowed to stop at every moment of the test, but were encouraged to restart as soon as possible. Covered distance after 6 minutes was measured to the nearest meter [22].

3.3 Strength

3.3.1 RM:

One Repetition Maximum (1RM) was determined bilaterally with the indirect Holten-method using commercial available stack weight and fitness equipment for biceps, triceps, leg press and adductors. A physiotherapist defined for each patient a test weight so that patients would be able to achieve maximal 6 to 12 repetitions. From this number of repetitions the 1RM was calculated using the Holten diagram depending on gender and type of muscles [23] . A global score for upper resp. lower limb strength was calculated by adding up the biceps brachii and triceps brachii scores resp. leg press and adductors.

3.3.2 Functional sit-to-stand test (STS):

The STS measures the maximum number of times within 30s that an individual can rise to a full stand from a seated position, without pushing off with the arms. The number of completed stands (up – down) is considered the participant’s score. This assessment is highly correlated with 1RM measurements and has high test-retest reliability (ICC=0.84 for men and 0.92 for women) [24].

3.3.3 Hand grip strength:

The participant is in a standing position, arms at his side, not touching the body. The elbow is in 90° flexion. The participant is asked to squeeze the dynamometer (Jamar) with as much force as possible, being careful to squeeze only once for each measurement. Three trials were made with a pause of about 10-20 seconds between each trial to avoid the effects of muscle fatigue. Left and right hand were alternated. The best score was registered.

3.3.4 Muscle fatigue resistance:

The participant is in the same position as described above (hand grip). He has to squeeze the dynamometer with as much force as possible and as long as possible. The test is finished when grip strength drops to 50% of its maximum during sustained contraction [25].

3.4. Preexercise and Postexercise Blood Glucose Monitoring

Capillary blood glucose was determined on a glucometer (One Touch Ultra, Lifescan) before and after each exercise session using blood drawn by a finger stick. To avoid hypoglycaemia and severe hyperglycaemia, guidelines from the Amercian Diabetes Association concerning blood glucose levels while participating in physical activities were followed [15] .

3.5. Quality of life (SF-36)

The General Health Survey Short Form (SF-36) measures perceived health in the areas of physical functioning, role-physical, bodily pain, general health, vitality, social functioning, role-emotional and mental health, with higher scores (range 0–100) reflecting better perceived health. The Dutch version of the SF-36 was used in this study [26].

4. Data-analysis

Data are expressed as median and range (minimum-maximum). Data were analyzed with a statistical software program (Statistical Package for the Social Sciences, SPSS 17.0, SPSS Inc, Chicago, IL, USA). To evaluate significant pre-post differences within groups Wilcoxon test was performed. To evaluate possible differences at baseline and the evolution between both groups Mann-Withney U-test was used. Significance level is set at $P<0.05$.

<u>Results:</u>

3.1 Baseline characteristics

Baseline clinical data are given in Table 1. No difference between the control and intervention group was present. In the training group 2 children were treated with a continuous subcutaneous insulin infusion (CSII), while the others and all control patients had multiple daily injections (MDI). In the training group 6 children used Actrapid® and 2 Novorapid®, 2 injected Levemir® and 4 Lantus®. In the control group 7 used Actrapid® and 1 Novorapid®, while 4 injected Levemir® and 4 Lantus®. Approval for this study was provided by the ethics committee of the Ghent University Hospital.

At baseline, there were no significant differences between the groups for all measured anthropometric data, physical fitness data, metabolic parameters and quality of life scores (SF-36) (table 1 and 2). Five participants of the training group had a normal weight and 3 had overweight, while in the control group 6 had a normal weight and 2 had overweight.

3.2. Participation in and acute and adverse effects of the training sessions.

In total 38 training sessions were organised. The median number of session participations was 24 with a minimum of 20 and a maximum of 32.

After the training sessions, the median number of hypoglycaemic levels was 3 with a minimum of 1 and a maximum of 6 for 7 out of the 8 children in the training group. One child had 15 low blood glucose levels in 31 training sessions. The glucose level of every child decreased after the training session. The median decrease of glycaemia after the training was 85 mg/dl with a minimum of 20 and a maximum of 130 mg/dl.

3.2 Training effects

Body size and body composition (table 1):

After twenty weeks, there was no significant change in body weight, BMI, waist circumference, fat mass and fat free mass in the experimental group as well as in the control group.

Physical fitness (table 1):

After the intervention period, muscle fatigue score, number of sit to stand, six minute walk distance, upper and lower limb strength increased significantly ($p<0.05$) in the training group, while no changes occurred in the control group.

PeakVO2, peak power and peak heart rate did not differ significantly in both groups. However, the ratio of peak oxygen consumption versus peak power decreased significantly in the training group ($P<0,05$), while it did not change in the control group.

Glycaemic control (table 2)

In both groups no significant changes were noticed for fasting glycaemia and HbA1c concentration. The total daily insulin dose decreased significantly ($p<0.05$) in the training group, while it remained at the same level in the control group. When expressed as per body weight, insulin dose significantly decreased in the training group, while it increased significantly ($p<0.05$) in the control group.

Quality of life (table 2)

We noticed no significant effects on the different subdomains of the quality of life, but in the domains general health, emotional functioning and vitality we could observe an important increase.

Discussion

The main findings of this study are that a 20 weeks combination (aerobic and strength) training have a tendency to be able to decrease the daily insulin dose , to ameliorate physical fitness and to have a slight, but positive impact on well-being in adolescents with type 1 diabetes. Individually, there is a large variability in outcome ranging from no effect to a large, significant effect on the different measured parameters.

There are contradictory data from studies dealing with the question whether supervised exercise training can improve glycaemic control in children and adolescents with type 1 diabetes. Although the half of patients in our study had a HbA1c value > 7.5 % , which is considered as an insufficient metabolic control, the median value of 7.9 % in the intervention group is consistent with the current metabolic control in adolescents in other European centres [27]. One might expected more impressive changes in those patients with higher HbA1c values at start.

Rowland et al. [12] and Zinman et al. [4], Landt et al. [11], Wallberg-Henriksson et al. [13], Laaksonen et al. [10] investigated the effect of endurance training on HbA1c levels but could not find significant effects. Ramalho et al. [15] reported also no effects on HbA1c, but noticed a reduction of the insulin dose after 12 weeks of strength training. Campaign et al. [8] and Dahl-Jorgenson et al. [9] using an aerobic training as well as Mosher et al. [16] after a combined aerobic and strength training program found a positive effect on glycaemic control. We could observe a slight decrease in the daily insulin dose, while in the controls there was an increase, but not a decrease in HbA1c levels. In patients with type 1 diabetes, as in individuals without diabetes, exercises increases insulin sensitivity and muscle glucose uptake [28]. Landt et al. [11] and Wallberg-Henriksson et al. [13] demonstrated an improvement of the insulin sensitivity measured by euglycaemic clamp. The lack of improvement in HbA1c in our study might be explained by the reduction in insulin doses and increased carbohydrate intake related to the hypoglycemic episodes that frequently occurred in these patients not only during training, but also up to 12 h after training 24. In our participants, the insulin dose was reduced based on their individual response to exercise, as determined by self monitoring blood glucose levels. The American Diabetes Association states that these adaptations are preferentially based on blood glucose monitoring in order to avoid hypoglycemia and does not provide specific cut-off values [15].

In our study, no significant effects could be noticed on BMI, body fat and/or fat free mass. Concerning the influence of exercise training on anthropometric indices literature data are not concordant. Some authors reported some positive effects on BMI, waist, fat mass and/or fat free mass [15,16], while other authors did not find any change of these parameters [4,8,9]. Besides methodological issues, differences in duration (ranging from 12 weeks to 6 months) frequency (2 to 5 times a week) and intensity of the training programs (endurance, strength or combination) might explain these discordant finding between studies. Differences between studies might also be explained by a different body composition status at start and be related to observed changes in insulin doses.

We noticed a significant amelioration of the ratio VO2/power in the training group. This indicates that the children who have exercised, uses less oxygen for a given workload, meaning that the exercising muscle of the diabetic adolescent is becoming more mechanically efficient [29]. PeakVO2, peak Watt and peak HR however did not change significantly. An improvement in cardiorespiratory endurance was also reported by Campaign et al. [8], Wallberg-Henriksson et al. [13] and Mosher et al. [16]. However, in these studies an improvement in peakVO2 was noticed, while this was not the case in our study. Dahl-Jorgenson et al. [9] found no increase in peakVO2 after 5 months training twice a week. This study is in line with our study, also regarding magnitude en frequency of training.

As expected, and in line with the study of Ramalho et al. [15], both upper and lower limb strength increased in the intervention group, while it remained almost stable in the control group. We found however that strength of lower limb muscles ameliorated much more than upper limb muscles. This can be explained by the fact that the training included cycling and stepping exercises besides the strength exercises and thereby addressed lower limb muscles even more explicitly. We cannot exclude that besides a training effect, there might have been an important learning effect. During the training program, adolescents learned to perform a correct start position for every exercise and as such got acquainted with appropriate technical performance in these exercise tasks.

We could observe a significant impact on functional testing. After training, mean 6MW distance increased significantly with 60m, which is a clinical relevant change [22]. Calders et al. [30] showed that this test is strongly influenced by BMI, strength of quadriceps and peakVO2 in overweight and obese children without diabetes type 1. In our study, we noticed a stable peakVO2 and BMI and a strong increase in quadriceps strength. The latter may contribute to the increased outcome.

The scores on the sit-to-stand test ameliorated significantly in the intervention group. As quadriceps strength is an important predictor for sit-to-stand scores, the increase of lower limb strength in this study can explain the increase [31].

We could not observe a significant change of the hand grip strength, but muscle fatigue resistance increased significantly in the intervention group. Hand grip strength is strongly associated with fat free mass [32]. Due to the fact that there was no significant change of fat free mass, this can account for this observation. We suspect that the increased muscle strength of upper limb and a better neurological functioning explain the increased muscle fatigue resistance [25].

Previously, Wiesinger et al. [19] reported improved subscores of quality of life, mainly in social functioning and vitality after training. In this study, patients trained for 4 months 3 times a week, which is more intensive than in our study and baseline scores of the QoL were also lower than in our study. Overall scores in our study were good to very good, as recently reported by Wagner et al. [18]. Only for general health, emotional functioning and vitality baseline scores were somewhat lower. In these subdomains, we could observe improvement.

Although at the physical and metabolic level there are significant effects, the amount of these effects is not large and is very variable. It is possible that this is due to the small sample size and the variable participation in the training sessions. Given the low participation in sports in diabetic adolescents and the more sedentary life style of adolescents general , we expected a low participation interest. Moreover, in most exercise reported exercise interventions reported in the pediatric literature , total number of participants was in most studies lower than 20. Travel problems , the limited days of scheduled exercise (3 times a week) and both the fear for hypoglycaemia and the recurrence of exercise-induced hypoglycaemic events in some patients were the major factors for irregular attendance . In adolescents involved in sports hypoglycemic episodes are reported more frequently than hyperglycemic ones [33].

While some adolescents have trained 32 out of the 38 times, other participants have trained only 20 times in this period, this is once a week. It is therefore possible that those who have trained 20 times in total, on average once a week, did not make any progression, while those who have trained more frequently (up to 32 times), will possibly have an exercise stimulus in the super compensation phase, which can result in a growth of fitness and metabolic adaptation. Extensive and intensive aerobic exercises will have a time to reach maximal super compensation from 8 to 30 hours, anaerobic exercises from 36 to 60 hours and strength training from 48 to 80 hours [34].

More thought is to be given how to encourage adolescents to participate in exercise programs. Personalizing the exercise program, more frequent reassessments of the guidelines for prevention of exercise induced hypoglycaemia and emphasizing not only the health promoting benefits, but also its effects on general well being might motivate more adolescents to start and continue exercising.

Conclusion

After aerobic and strength training for 20 weeks there is a tendency that this training mode is able to lower daily insulin requirement, to improve physical fitness and resulted in a tendency towards better scores on general health, vitality and role emotional. These results are promising enough to encourage vigorous physical exercise, in adolescents with type 1 diabetes, given their expected positive impact on cardiovascular risk on the long term.

Clinical messages

- In adolescents with diabetes type 1 combined aerobic and strength training has a tendency to be able to:
  - lower daily insulin requirement
  - improves physical fitness
  - generate positive effects on well-being
  - Given the expected positive impact on cardiovascular risk on the long term, we may encourage combined exercise training.

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