FULL TITLE: Exercise to preserve beta cell function in recent-onset type 1 diabetes mellitus (EXTOD) - a randomized controlled pilot trial

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Novelty statement

- We show that it is possible to recruit and randomise people with newly-diagnosed T1DM to a trial of an exercise intervention and increase and maintain their exercise levels over 1-year. Our findings contradict the only other study in T1DM adults, which did not show an increase.

- We also show that an exercise programme is safe and can be undertaken without hypoglycaemia or injury, and appears to improve physical fitness, insulin-sensitivity, and reduce insulin-requirements.

- We objectively measure physical activity in newly diagnosed people with T1DM and show them to undertake more physical activity than previously reported.

- In the setting of a pilot feasibility trial, the rate of loss of beta cell function does not appear to be influenced by exercise. However, the increased insulin sensitivity associated with exercise may have influenced the validity of meal stimulated increases in plasma C-peptide concentration as a measure of residual beta-cell function.

ABSTRACT

Aims

Residual beta-cell function is present at the time of diagnosis with type 1 diabetes (T1DM). Preserving this beta-cell function reduces complications. We hypothesised that exercise preserves beta-cell function in T1DM and undertook a pilot trial to address the key uncertainties in designing a definitive trial to test this hypothesis.

Methods

A randomised controlled pilot trial in adults aged 16-60 years diagnosed with T1DM within the previous three-months was undertaken. Participants were assigned to control (usual care) or intervention (exercise consultation every month), in a 1:1 ratio for 12-months. The primary outcomes were recruitment rate, drop out, exercise adherence (weeks with >=150 minutes of self-reported moderate to vigorous physical activity (MVPA), and exercise uptake in the control group. The secondary outcomes were differences in insulin sensitivity and rate of loss of beta-cell function between intervention and control at 6 and 12-months.

Results

Of 507 individuals who were approached, 58 (28 control, 30 intervention) entered the study and 41 completed it. Participants were largely white European males, BMI 24.8$\pm$3.8Kg/m^2, HbA1c 9$\pm$2% (75$\pm$25mmol/mol). Mean level of objectively measured MVPA increased in the intervention group (mean 243 to 273 minutes/week) and 61% of intervention participants reached the target of greater than 150 minutes/week of self-reported MVPA on at least 42 weeks of the year. Physical activity levels fell slightly in the control group (mean 277 to 235 minutes of MVPA/week). There was exploratory evidence that intervention group became more insulin sensitive and required less insulin. However, the rate of loss of beta-cell function appeared similar between the groups, although the change in insulin sensitivity may have affected this.

Conclusion

We show that it is possible to recruit and randomise people with newly-diagnosed T1DM to a trial of an exercise intervention and increase and maintain their exercise levels for 12-months. Future trials need to incorporate measures for greater adherence to exercise training targets, and include more appropriate measures of beta-cell function.

ABBREVIATIONS:
AUC: Area under curve
EXTOD: Exercise for Type One Diabetes
GAD: Glutamic acid decarboxylase
IA-2: Tyrosine phosphate-like antigen
RCT: Randomised Controlled Trial
MVPA: Moderate to vigorous physical activity
T1DM: Type 1 diabetes
T2DM: Type 2 diabetes
ZNT8: Zinc transporter

INTRODUCTION

Type 1 diabetes (T1DM) is characterised by autoimmune destruction of pancreatic insulin-secreting beta cells [1]. Significant numbers of beta cells are present at the time of diagnosis with T1DM [2], but these numbers and their function continue to decline following diagnosis. The preservation of beta cell function has important clinical benefits. Data from the Diabetes Control and Complications Trial (DCCT) has demonstrated that a meal-stimulated 90 minute C-peptide value of greater than 200 pmol/L is associated with improved glucose control, reduced risk of retinopathy and nephropathy, and with more than a halving of rates of hypoglycaemia [3]. Therefore interventions that can preserve residual beta cell function in new onset T1DM are clinically needed. Furthermore therapies proven to preserve beta cell function in new onset T1DM can be taken forward into trials of T1DM prevention.

Clinical trials of medicinal agents for beta cell preservation in new onset T1DM have been ongoing for over three decades. None as yet have shown significant and sustained clinical benefit [4]. Furthermore the adverse side effect profile of some of these agents requires a considered and cautious roll out [5]. Whilst these medicinal agents continue to need to be investigated, we also need to explore new therapies with an acceptable side effect profile, and which have the potential to be used as an adjunct to the agents under investigation.

We have previously outlined the rationale for physical exercise as a modifier of beta cell loss, and one that should be trialled in new onset T1DM [6]. In this review we presented data from studies showing that physical exercise preserves beta cell function in animal models of type 1 and type 2 diabetes, in healthy humans, and people with impaired glucose tolerance and with type 2 diabetes (T2DM). For example, the STRRIDE study demonstrated that an 8-month walking exercise programme of an hour three times a week in people at risk of T2DM improved beta cell function by 60% [7]. These findings have not been tested in people with T1DM. In our commentary, we also outlined some of the mechanisms of increased beta cell proliferation and decreased beta cell loss through which this benefit may occur. We went on to outline the need for a prospective clinical trial to test the hypothesis that exercise preserves beta cell function in people newly diagnosed with T1DM.

We undertook a pilot trial to address the key uncertainties in designing a definitive trial to test the hypothesis that exercise preserves beta-cell function in new onset T1DM.

Prior to this pilot trial we undertook a qualitative study to identify barriers to the uptake and adherence to an intensive exercise programme. Here, we present the results of the subsequent pilot randomised controlled trial (RCT) involving an exercise intervention in people with recent onset T1DM. We decided that the exercise intervention should be non-supervised because the patients who helped us to design the study felt that a 12-month supervised exercise programme would be too onerous. In addition we have shown that with non-supervised exercise programmes we can increase and maintain exercise level in a variety of people with chronic diseases including people with newly diagnosed T2DM [8,9,10].

Specific objectives of this pilot RCT were to:

1) Determine the proportion and characteristics of people with T1DM who would be willing to take part in an RCT of exercise (that is, recruitment rate).
2) Define the rates of adherence to a non-supervised exercise intervention and participant drop-out.
3) Determine the rate of exercise uptake in the non-intervention arm (that is, intervention contamination).
4) Determine the rate of loss of beta cell function in the intervention and control arm to enable the statistical power calculations for the subsequent definitive trial to be refined.
5) Determine (as a secondary outcome) whether the 12 months exercise intervention results in a significant preservation of beta cell function.
6) Develop estimates of statistical properties of potential outcome measures that are needed for sample size calculations for the definitive trial.

RESEARCH DESIGN AND METHODS

The protocol for the EXTOD trial study has previously been published [11].

Trial Design

This pilot study used a multicentre, parallel-group, randomised controlled trial design. The study was approved by the Birmingham East, North and Solihull Research Ethics Committee (0/H1206/4), UK, and all participants provided written informed consent.

Participants

The study was open for recruitment between November 2011 and January 2014. Clinical staff at 19 UK NHS hospitals identified people newly diagnosed with T1DM and provided them with information about the study. Eligible participants had a clinical diagnosis of T1DM, were over 16 at diagnosis and were self-administering their insulin as part of a multiple dose injection regime. Exclusion criteria were age older than 60, diagnosed with T1DM more than 3 months, C-peptide less than 200pmol/L at 90mins following meal stimulation, uncontrolled blood pressure, pregnancy or planning pregnancy, unable to increase exercise levels and therapy that affects heart rate (beta blocker, calcium channel antagonist) because this would affect the ability to estimate VO_2max (maximum oxygen consumption) and monitor exercise intensity using heart rate monitors.

Randomisation

All eligible participants were randomised in a 1:1 ratio to intervention (exercise training plus usual care) or control (usual care alone) groups. Randomisation was stratified by site and minimised on 90 minute stimulated C-peptide level and estimated VO_2max. Randomisation was organised and supervised through the University of Birmingham Primary Care Clinical Trials Unit, UK, using an on-line randomisation programme with a telephone service used as a back-up. The study

dietician performed randomisation at visit 4, after standardised dietary advice had been given. Dietitians, nurses, and participants were aware of allocation, but doctors were not. Nurses did all assessments.

Procedures

Using goal-oriented motivational interviewing techniques, participants in the intervention group were encouraged by the research nurse to safely increase their exercise levels according to a graded program to at least 150 minutes per week of moderate to vigorous intensity exercise in bouts of at least 10 minutes, aiming for 240 minutes per week of exercise [11]. Each patient was given a wrist-worn heart rate monitor (Polar, Warwick, England) and physical activity log to record the length of exercise and the heart rate during exercise and blood glucose before and after exercise. These logs were discussed with the research nurses and used to help monitor and encourage an increase in exercise levels. The aim was to increase exercise over the first 12 weeks of the study and then to maintain exercise levels for the remainder of the study. Any form of exercise could be undertaken and exercise could be accumulated throughout the day in bouts of at least 10 minutes. Participants met with the nurse for 20 minutes to discuss their exercise levels at 2, 4, 8, 12, 16, 20, 30, 36, and 42 weeks as specified in the protocol. Using a protocol similar to this we have shown that we can increase and maintain exercise levels in a variety of patients with chronic diseases including patients with newly diagnosed T2DM [8,9,10].

Usual care consisted of standard dietary and exercise advice after randomisation and at the end of the study, with reviews by a study doctor and nurse at baseline and at 6 and 12 months and review by a nurse alone at 3 and 9 months. Both intervention and control group received usual care. The exercise advice in the usual care arm was the provision of the local hospital document on exercise and T1DM, and advice on the importance of exercise.

Management of diabetes, blood pressure, and lipid profile was undertaken by the study team for the period of the trial. Any changes in treatment of these factors were made by a doctor unaware of treatment allocation, and according to a strict trial protocol, to keep the risk of performance bias to a minimum.

Measures were taken at baseline (pre-randomisation) and at 6 and 12 months post-randomisation. Beta cell function was assessed using a 240 ml Fortisip mixed meal tolerance test (MMTT) with blood taken for C-peptide at -10, 0, 15, 30, 60, 90 and 120 minutes. Measures of health-related quality of life (EQ5D, CES D, WHOQOL), diabetes distress (PAID, Illness perception), sleep quality (PSQI), exercise motivation and self-efficacy (Bandura, Deci and Ryan, outcome expectation for exercise), and diet (Toole and Glasgow) were assessed through questionnaires as outlined [11]. Fitness (predicted VO2max) was assessed by two methods (Astrand-Ryhming and YMCA/ACSM) during a single exercise test undertaken on a calibrated cycle ergometer. Therefore, we undertook one exercise protocol, and applied two different algorithms to the same data. The mean of these two values was taken as the final measure of fitness. We opted to use a combination of two methods to

reduce the error of estimated maximum oxygen uptake from these two predictive tests. Whilst both these techniques are widely used and well-established, each technique is based on different assumptions and thus a combined estimate across both predictors will have lower error than relying on one estimate alone. In order to assess changes in objectively measured habitual physical activity, participants wore an accelerometer (GT1M; ActiGraph LLC, Pensacola, FL, USA) for 7 days on a belt around the waist, except when swimming, bathing and sleeping. Accelerometers were set to record data every minute. Raw accelerometer files were processed using KineSoft (version 3.3.62; KineSoft, Saskatoon, SK, Canada). A valid day was defined as recording at least 8 h of measurement, excluding periods of ≥20 min with continuous zero values (considered to be non-wear time). Total physical activity was computed as the mean accelerometer cpm over the full period of valid recording. The average number of minutes of moderate to vigorous physical activity (MVPA) per valid day were computed using a threshold of ≥1,952 cpm, equivalent to an exercise intensity of greater than 3 metabolic equivalents (METs) [12]. For inclusion in analyses, participants were required to record at least three valid days of accelerometer data.

C-peptide and insulin were measured using a direct electrochemiluminescence immunoassay by the University of Exeter as previously described [13]. The limit of the C-peptide assay is 3.3 pmol/L and the insulin assay 1.39 pmol/L. Antibodies were measured at the Research Laboratories of the School of Clinical Sciences, University of Bristol (Southmead Hospital, Bristol, UK).

Sample size

Thirty participants per arm were considered sufficient to achieve the feasibility objectives of this pilot study. An initial recruitment rate of 30% was anticipated followed by a 90% adherence rate to the exercise schedule and a 15% drop-out rate.

Statistical analysis

Descriptive analysis for demographic and outcome measures are presented in terms of their arithmetic mean and standard deviation (sd) range by group in Table 1.

Relevant variables have been presented as baseline adjusted mean, with standard deviation and 95% confidence intervals. In accord with the CONSORT extension for pilot studies and that we were not formally powered to detect differences in outcomes between groups, we have not calculated or presented p values [14].

Recruitment rates were calculated as the percentage of people with T1DM who were contacted about the study and who consented to be involved. Adherence to exercise in the intervention group was assessed using the exercise diaries through looking at how many weeks participants reported doing more than 150 minutes per week of MVPA in bouts of at least 10 minutes. We considered success as at least 80% of patients doing more than 150 self-reported minutes a week of exercise for 42 weeks of the year. Forty-two weeks was picked because they will not reach 150 minutes per week until week 10 into the intervention if their exercise levels were low when joining the study. The physical activity of the intervention and control

group was also assessed from the Actigraph accelerometer measures at baseline, 6 and 12 months. Withdrawal rates were calculated as the percentage of consented participants who were lost to follow up at 12 months.

As per recommended guidelines for trials of beta cell preservation [15], beta cell response was estimated as area under curve (AUC) C-peptide and calculated for each participant applying the trapezium method [16]. Measured C-peptide values are non-zero and simulation studies suggested that integrals estimated from trapezoidal rule outperformed all other methods when function values are non-zero [17]. The 'minus 10' minute and 'zero' minute measure for C-peptide level was averaged to obtain the pre-meal baseline level of C-peptide and the subsequent measures were used to calculate total AUC for each participant. The subject specific AUC was further divided by 120 to obtain average AUC per minute for each person and is expressed in pmol/L. The outcome variable AUC was skewed and a log transformation with natural base was needed for regression models. The results are presented as exponentiated coefficients.

Our analyses included all participants with complete data and based on intention to treat approach i.e. comparison of groups by initial random allocation. For all anthropometric, biochemical and psychometric variables, we developed separate analysis of covariance (ANCOVA) model adjusted for their baseline score to compare groups at 6/12 months and reported with standard errors (s.e.) and 95% CIs. For C-peptide AUC, the model was further adjusted for other baseline covariates, i.e. age, sex, HbA1c, GAD-titre/IA2A-titre/Znt8-titre positivity, baseline MVPA and VO_2max. The titre of GAD antibodies in particular is associated with more rapid rates of beta cell loss and it is important that this is adjusted for in the AUC analysis [18].

All analyses were undertaken using statistical software Stata, version 14.2 (StataCorp. 2015. *Stata Statistical Software: Release 14*. College Station, TX: StataCorp LP).

Role of the sponsor

The sponsor of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

RESULTS

Participants and characteristics

A total of 507 adults with new onset T1DM were identified, of these 214 were assessed for eligibility for this study. Eighty-six were eligible for face-to-face screening, and of these 15 participants were recruited into a distinct but linked study exploring barriers to exercise in newly diagnosed T1DM, and 58 participants were randomised (see Fig 1).

The baseline characteristics are shown in Table 1. The population was largely white Caucasian, with twice as many males as females. The population were of a healthy

body mass index (BMI). A third of the participants tested negative for all three islet autoantibodies tested.

There was evidence of baseline differences between group in sex, GAD-titre positivity and number of positive antibodies whilst other factors appeared balanced.

Drop out and adherence

Of the 58 participants randomised, 41 completed the study (see Fig 1). The most common reason for withdrawal from the study was lack of time due to family and/or work commitments. Most withdrawals (11/17) were within one month of study entry. Withdrawal rates were equal across the control and intervention arms (29% and 30% respectively).

Adherence to visits of those that remained in the study was good with the average attendance at each visit being 86%, and 78% of participants attending all or missing just 1 of their required visits (8 in the usual care arm and 17 in the intervention arm).

Participants self-reported exercise diaries showed that at baseline, only 16% of the participants on the intervention group were reaching the target of 150 minutes a week of moderate intensity exercise in bouts of more than 10 minutes. This increased from 16% to 61% at the end of the study. For participants in the control group, the exercise diaries showed that 21% of were reaching the 150 minutes target at baseline as 10min bouts. The control group did not keep an exercise diary across the study because doing so has been shown to increase activity levels. The control group however completed the exercise diary at study completion at 12 months and this showed a fall to only 12% of participants reaching the 150 minutes target as 10 min bouts.

Physical activity

Of the 58 participants who entered the study, 49 had valid accelerometer data at baseline, 33 had valid accelerometer data at 6 months, and 30 had valid accelerometer data at 12 months. Of these, 26 had valid accelerometer data at all three time points. At baseline, participants in the intervention group undertook an average of 243 (sd $\pm$141) minutes of MVPA per week (Fig 2, supplementary Table 1). This increased to a mean of 285 (s.e $\pm$40) minutes at 6 months, and mean of 273 (s.e $\pm$34) minutes at 12 months. This increase in activity was associated with an increase in predicted VO_2max of 10% (from 32 sd $\pm$6 to 35 se $\pm$1 ml/kg/min) over the 12 months (supplementary Table 1). Control group participants showed no evidence of intervention contamination with their average MVPA per week dropping from 277 (sd $\pm$153) to 235 (se $\pm$36) minutes when measured by actigraphy. There was also a reduction in predicted VO_2max (from 35 sd $\pm$10 to 34 se $\pm$2 ml/kg/min) over the 12 months (supplementary Table 1).

Beta cell function

The overall unadjusted mean AUC C-peptide dropped across participants from 993pmol/L to 883pmol/L over the 12 months (11% fall). Estimated mean C-peptide

AUC from fully adjusted model showed no difference between the intervention and control groups (Supplementary Table 2), and this applied to the whole group (Fig 3c) as well as the antibody positive group (Fig 3d).

To investigate the relationship between the AUC C peptide measure of beta cell function and changing insulin sensitivity, we explored whether those subjects who became most insulin sensitive also appeared to 'lose' most C peptide. Supplementary figure 1a illustrates change in AUC C peptide against change in insulin resistance, showing that decreasing insulin resistance associates with a 'fall' in AUC C peptide measure of beta cell function. To adjust for the effect of insulin sensitisation on accuracy of the stimulated C peptide test, we calculated the disposition index. This is a measure of beta cell function that takes into account insulin resistance [19]. It has been used in human studies of T2DM that demonstrate a beta cell preserving effect of exercise [17]. Quantifying beta cell function using the disposition index demonstrates preservation of beta cell function in the intervention group, but a fall in the control group (supplementary figure 1b).

Metabolic variables

There was evidence of reduction in HbA1c and increase in weight in both groups during the study, as would be expected in patients with initiation of insulin therapy following diagnosis with T1DM. There did not appear to be a difference in mean HbA1c between groups at 6 or 12 months. There was a trend toward a reduction in diastolic blood pressure, triglycerides and LDL cholesterol at follow up in the intervention group (supplementary Table 2). There was also a trend to increased HDL with intervention that was not seen in the control group

The intervention group showed improvement in markers of insulin sensitivity that were not evident in controls. Injected insulin doses decreased and insulin resistance fell in the intervention group, and these benefits were not seen in the controls (Fig 3).

Adverse events

There was no difference between groups with regard to the total mean number of reported mild hypoglycaemia (14.6$\pm$15.2 versus 15.1$\pm$12 per year) or severe hypoglycaemia requiring third party intervention (one in each group) over the year study. There was also no difference in the mean rates of adverse events between the two groups (1.5$\pm$1.5 versus 1.8$\pm$1.3 per year).

Quality of life, diabetes distress, fear of hypoglycaemia and exercise

The self-efficacy scores, hypoglycaemia worry, hypoglycaemia behaviour and perception of the healthcare climate appeared to be higher for the intervention group compared to the control group at 12-month (supplementary Table 3). However the slight fall in depressive symptoms seen in the control group was not seen in the intervention group.

DISCUSSION

We were able to meet our pilot trial objectives. We found that 11% of adults identified with newly diagnosed T1DM were willing to take part in this study, that 29% subsequently dropped out, that 61% of participants reached the exercise target of greater than 150 minutes/week of moderate intensity exercise on at least 42 weeks of the year, and that there was no evidence of exercise uptake in participants allocated to the control group. We also show that people with T1DM who would be willing to take part in a trial of exercise are largely white European males of healthy BMI, a mean age of 32 years, and a third test negative for islet autoantibodies.

We show for the first time that an unsupervised exercise programme can increase physical exercise levels of moderate intensity and above in adults newly diagnosed with T1DM by 30 mins per week and maintain this over 12 months. This is in contrast to the control arm where there was a fall in physical activity levels by 42 mins per week over the equivalent period. We also show that this exercise programme is safe and can be undertaken without hypoglycaemia or injury, and appears to improve physical fitness, insulin sensitivity, and reduce insulin requirements. We would caution that the submaximal VO_2max protocol used to estimate fitness is reliant on heart rate and has not been validated in a T1DM population. However, autonomic dysfunction is unlikely in a newly diagnosed T1DM patient and therefore we would propose that the estimates of VO_2max are likely to be reliable.

Also in the context of a feasibility study, using standard measures of beta cell function, our data does not prove that the exercise programme preserves beta cell function.

These findings will be used to help design future studies to determine whether exercise preserves beta cell function in adults newly diagnosed with T1DM. However some aspects of the data from this trial are worth discussing in greater detail, both to aid refining future intervention trials, and because it provides details of the characteristics and natural history of adults newly diagnosed with T1DM.

This is the first study to demonstrate that an unsupervised exercise programme can increase and maintain physical exercise in adult people with T1DM. In the PEP-program, the only other unsupervised exercise programme for adults with T1DM, activity was not increased [25]. In four studies of unsupervised exercise studies in adolescents and/or children, two showed an increased activity at 3-4 months and two did not [26]. The results of our study are consistent with studies in adults with T2DM where others and we have demonstrated that an unsupervised exercise programme can increase and maintain physical activity for a year and longer [9,27]. Furthermore, the increase in moderate to physical activity in our study is similar to that which we have demonstrated in adults with newly diagnosed T2DM [9]. Adherence to our exercise targets was less than reported in other studies with only 61% of participants obtaining our minimal exercise target. We had hoped to increase the volume and intensity of exercise more than was observed. Further research on exercise adherence, and obtaining higher intensity and volumes of exercise is required in adults with T1DM.

We also believe this to be the first study to objectively measure physical activity in newly diagnosed people with T1DM. Studies of people with long standing T1DM where physical activity was self-reported suggested 36-44% of them were doing less than 1 session of exercise per week [20, 21]. In our study of exercise in people with newly diagnosed T1DM, objectively measured MVPA was 285 mins per week, much higher than previously reported. This may not represent all newly diagnosed T1DM adults because people with an exercise interest are preferentially attracted to participate in such studies. However, these activity levels are similar to healthy non-diabetic people in the US [22], and less than that seen in participants in UK Biobank study [23] and in a cross section study of people in Bristol, UK [24]. Regardless, we were surprised that the mean level of physical activity was only 37 mins/day which is only 11 minutes per day more than newly diagnosed people with T2DM who were twice as old [9].

Although we were not formally powered to compare groups, improvement in metabolic variables with exercise detected in our study is broadly similar to those already reported (reviewed in Chimen et al [28]). Our study detected improvements in mean HDL of 4.7% (8-30% in published studies), triglyceride of 10% (13-15% in published studies), and insulin resistance of 20% (up to 23% in published studies). In line with other studies, there was no improvement in glycaemic control with exercise [29].

The C-peptide fall of 11% in our study was lower than rates of 25% fall in the year following diagnosis reported in other studies [30]. This may be contributed to by the older age of our participants because older age has been associated with a more gradual fall in C peptide [1,2,3].

The secondary outcome measure of beta cell function measured by AUC C-peptide did not differ between the intervention and control groups. This may be because sufficient volume or intensity of exercise was not achieved. Whilst some of the studies demonstrating an improvement in beta cell function with exercise observed exercise levels of over 200 mins MVPA (achieved by many of our participants), others reported a greater than 300mins per week [6]. Intensity of the exercise may also be important. In animal studies and studies of people at risk of T2DM, moderate intensity exercise preserves beta cells to a greater extent than high intensity [7,31]. For this reason our protocol was designed to increase levels of moderate intensity exercise. If the mechanisms (immunity, hormones, cytokines) underlying the protective effective of exercise differs between T1DM and T2DM, different intensities may need to be targeted for beta cell preservation in a T1DM population. Further studies into the efficacy of different exercise intensities and volumes on beta cell function in T1DM will be needed to determine this.

Another reason why a difference in AUC C-peptide was not seen between the two groups may be that this measure under-estimates beta cell function in the face of increasing insulin sensitivity [6]. Less insulin is required for glucose homeostasis in an

insulin sensitive state. Therefore when beta cell function is stable, an insulin sensitising intervention will result in a fall in the AUC C-peptide measure. It would be incorrect to interpret this fall in AUC C-peptide as a fall in beta cell function, but rather as an adaptive decrease in insulin secretion for the increasing insulin sensitivity. The analysis in supplementary figure 1 supports the concept that an increase in insulin sensitivity associates with an appropriate decrease in the AUC C peptide measure of beta cell function. This association therefore makes it difficult to use the AUC C peptide as an accurate measure of beta cell function in interventions that alter insulin sensitivity. Therefore beta cell outcome measures for exercise studies in T1DM need to account for the effect of exercise on insulin sensitivity. In our study, the intervention group maintained their AUC C-peptide measure despite becoming more insulin sensitive, consistent with this group effecting a 'real' increase in beta cell function. Exercise interventions for preservation of beta cell function in T2DM that have not accounted for changes in insulin sensitivity have provided conflicting results [32], whereas studies that have accounted for insulin sensitivity change have reported more consistently [33]. We have used disposition index in the further analysis of our data because it is an established measure of beta cell function that models for insulin sensitivity [17,19]. Whilst this approach to measuring beta cell function has not been validated in T1DM, its use suggests that in our study, beta cell function corrected for improved insulin sensitivity is preserved with exercise (supplementary figure 1).

The dropout rate of 29% in this study is about twice that originally predicted in the study design, and that described in studies of immunotherapeautic agents for new onset T1DM [34]. Our previous study of exercise intervention in people with newly diagnosed T2DM only reported a 3% dropout rate [9]. However this current study population was younger and in full time employment. Higher dropout rates have been reported in other exercise studies. In a recent meta-analysis of unsupervised exercise programmes, 20% of studies had greater than 20% dropout, 32% between 10 and 20% dropout, and 48% less than 10% dropout rate [35]. It is relevant that most of the dropouts were due to lack of time, and within the first month. We have undertaken qualitative interviews with our trial participants around trial retention. A clearer description of the time commitment required for such a study, more flexible appointments, improved feedback of results, more consistent healthcare support, and a prolonged 1 month 'run-in' phase may address this high dropout rate.

In summary, we have shown that it is possible to recruit newly diagnosed people with T1DM to an exercise study. We have also shown that we can safely increase and maintain exercise levels in these participants and that this is not deleterious to beta cell function. We believe it is now important to take forward this pilot study with a fully powered trial to definitively confirm whether exercise training can preserve beta cell function in T1DM. Exercise training is likely to be an affordable intervention that can be undertaken without significant adverse events, has many parallel benefits (cardiovascular risk, well-being, increasing insulin sensitivity etc), and can be used as an adjunctive therapy. However, this pilot study highlights that prior to undertaking full trial, we need to confirm the optimum approach to measuring beta cell function in an environment of changing insulin sensitivity, and improve our non-

supervised exercise programmes so we can maintain greater adherence to exercise in adults with T1DM.

Contribution statement

RCA, PN, MM and RST had full access to the primary data. RCA and PN led decisions about content and submission. All authors contributed to data analysis and interpretation, and the writing and editing of the report. All authors approved the final version of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

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Duality of interest

RCA has received honoraria from Novo Nordisk, Sanofi-Aventis, and Merck Sharp & Dohme, and travel expenses from Sanofi-Aventi. PN has received honoraria and travel expenses from Novo Nordisk, Sanofi-Aventis and Lilly.

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Figure legends

Fig 1: Consort diagram
Flow of participants through the EXTOD trial.
*Reasons for ineligibility in the 128 patients were: too long since diagnosis n=19, type 2 diabetes n=18, deemed unsuitable by investigator because unwell or other reasons n=16, outside age range n=8, unable to exercise n=6, planning to move away n=6, recruited to another RCT n=4, pregnancy or postnatal or childcare issues n=4, diabetes secondary to pancreatitis n=1, other n=25, not known n=21

Fig 2: Physical activity and Fitness
Physical activity was estimated as minutes per day of moderate to vigorous physical activity (MVPA) measured by actigraph. Accelerometer counts were converted to MVPA using widely accepted thresholds as described in the manuscript text. Briefly, each 60 second epoch where counts exceeded 1951 was considered to be MVPA. Physical fitness was measured by VO_2max (ml/kg/min) measured by cycle ergometer. Both were adjusted for age, sex and baseline score.

Fig 3: Metabolic variables
a) Total insulin doses administered by participants are displayed as dose per Kg of body weight and adjusted for baseline score. All participants were on a multiple dose insulin regime with analogue insulins.
b) Insulin sensitivity estimated by HOMA-IR calculated from endogenous peripheral blood insulin and glucose concentrations. The insulin assay does not cross react with exogenous insulin.
c+d) Beta cell function in all patients (c), and in those patients positive for any islet antibody (d)
Beta cell function estimated through meal stimulated C-peptide responses at baseline, 6 and 12 months for participants in the Control and Intervention arms. The C-peptide response is calculated as the 'area under the curve' (AUC) over a 120min period following a standard meal stimulus. Values are adjusted for baseline C-peptide, sex, age, baseline HbA1c, GAD and ZnT8 antibody titres, number of autoantibodies, baseline VO2max and baseline MVPA.

Supplementary Fig 1
a) Relationship between change in insulin resistance and change in beta cell function as measured by meal stimulated AUC C peptide in the Intervention and Control group, and with all subjects combined. Here, a positive change in the HOMA-IR (*x-axis*) indicates an increase in insulin resistance, and a positive change in C peptide (*y-axis*) indicates an increase in meal stimulated insulin secretion
b) Beta cell function as represented by mean disposition index in patients from the Control and Intervention groups. 6m and 12m group means are estimated after adjusting for baseline disposition index. The Disposition index provides an estimate of beta cell function adjusted for changes in insulin resistance and is calculated as HOMA-B x HOMA-S, where HOMA-B is the beta cell function and S is the insulin

sensitivity (https://www.dtu.ox.ac.uk/homacalculator/). (Intervention group had a lower mean disposition index both at baseline and 6-month (Baseline: Δ -1026, 95% CI: -3219 to 1167; 6-month: Δ -317, 95% CI: -2133 to 1499) but experienced a greater change by 12-month (12-month: Δ+848, 95% CI: -596 to 2291).